Reassessing the Role for Sympathetic Neurolysis in Patients with Pancreatic Cancer

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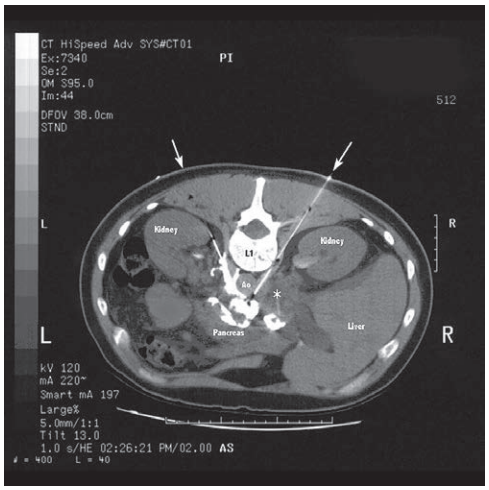
How and when to use sympathetic neurolysis, including neurolytic blocks of the splanchnic nerves and celiac ganglia, to provide pain relief for patients with adenocarcinoma of the pancreas remains a topic of ongoing debate. The literature consistently shows that sympathetic neurolysis offers effective, clinically meaningful pain relief to patients with moderate to severe pain associated with advanced pancreatic cancer and that this treatment reduces the dose of opioid analgesics needed to effectively control pain for some period. However, many questions remain: Does treatment impact quality of life? What is the best technique? When should the block be performed? Is survival affected?



"…what is the best role for sympathetic neurolysis in the management of pain associated with pancreatic cancer…?"

In this issue of Anesthesiology, Dong *et al.*[1] examine pain relief, survival, and quality of life in patients with unresectable pancreatic cancer after neurolytic splanchnic nerve block in a rigorously conducted, randomized, sham-controlled, multicenter trial. Their study offers intriguing insights and raises new questions about when to use sympathetic neurolysis in treating pain in patients with advanced pancreatic cancer. The greater lesser and least splanchnic nerves traverse over the anterolateral surface of the 12th thoracic vertebra. The splanchnic nerves carry sympathetic nerve signals to and from the celiac ganglia, which lie anterolateral to the aorta, nested around the celiac artery at the level of the first lumbar vertebra. Various techniques for neurolysis have been developed. Neurolytic splanchnic nerve block refers to a technique in which neurolytic solution—typically absolute (95%) ethanol—is placed posterior to the aorta over the anterolateral surface of the 12th thoracic vertebra. Splanchnic nerve block is typically carried out with percutaneous needle placement using fluoroscopic or computed tomography guidance. Neurolytic celiac plexus block is carried out by placing neurolytic solution anterolateral to the aorta at the L1 vertebral level, surrounding the celiac artery. Neurolytic celiac plexus block can be carried out under direct visual needle placement during surgery, percutaneously, or endoscopically through the wall of the duodenum using ultrasound guidance. There have been no direct comparisons of the clinical effectiveness of these different approaches, and for this discussion, we will assume that they all accomplish the same goal of interruption of the sympathetic innervation that mediates pain from visceral organs between the gastroesophageal junction and the splenic flexure of the colon.

Investigators in this new study[1] randomized 96 patients with stage III or IV pancreatic cancer to receive computed tomography guided splanchnic nerve blocks with 48 receiving absolute alcohol and 48 receiving saline. All patients were followed for 8 months after treatment and monthly pain scores, opioid consumption, and quality of life scores using the 36-Item Short Form Survey Instrument (SF-36) were reported. All patients had ongoing access to treatment with systemic opioids using a standardized dosing regimen. Neurolysis resulted in a statistically significant reduction in pain, but the magnitude of change was small and of limited duration (largest at the first month; mean difference in Visual Analog Scale on a 10-point scale, 0.7 [95% CI, 0.3 to 1.0]), with the advantage of neurolysis over systemic opioids vanishing by 4 months after the block. Reductions in opioid dosing were significantly greater after neurolysis when compared to systemic analgesic therapy alone for the first 5 months after treatment (largest at the first month;

Image: J. P. Rathmell.

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mean difference, 96 oral morphine milligram equivalents [95% CI, [68 to 124]). There were no significant differences in quality-of-life measures with neurolysis *versus* systemic therapy alone. There were no severe complications related to neurolysis, but transient orthostatic hypotension (60.4%), lethargy (56.3%), exhaustion (52.1%), and transient diarrhea (1 to 3 days, 29.2%) were common and prolonged orthostatic hypotension (more than 3 days, 12.5%) and diarrhea (more than 3 days, 10.4%) were not infrequent. These findings confirm those reported in a recent systematic review[2] and this trial joins three other high-quality clinical trials with similar findings.[3–5] Splanchnic or celiac plexus neurolysis is a relatively simple procedure, typically done on an outpatient basis, that leads to reduction in pain and opioid dosing, commonly leads to transient orthostatic hypotension and diarrhea, but has little or no impact on the overall quality of life of those treated.

The secondary outcome reported in this new study raises concern.[1] There was a significant reduction in survival in those who received splanchnic or celiac ganglion neurolysis *versus* control, and further analysis suggested the survival reduction was significant only in those with more advanced disease (stage IV). How do we interpret those findings? First, it is important to acknowledge that the study was not powered to detect differences in survival and thus this is a secondary, exploratory outcome that will need verification in future studies. Previous reports on the impact of neurolytic celiac plexus block on survival have been mixed. The story begins with a report by one of the authors of this editorial. In 1993, Lillemoe *et al.*[6] reported the results of a randomized trial of chemical splanchnicectomy performed intraoperatively, with 65 patients receiving alcohol neurolysis and 72 patients receiving the placebo. Mean pain scores were significantly lower among those receiving neurolysis than control through 6-month follow-up and those patients with preexisting pain who received neurolysis showed a significant improvement in survival and overall well-being when compared with controls. Of note, none of these patients had known stage IV cancer; these patients had cancer that was considered potentially resectable until metastases/vascular invasion was seen once the surgery had begun. Focusing on more recent, high-quality evidence, including the new study that appears in this issue,[1] leaves us with a very different picture. In 2004, Wong *et al.*[3] randomized 100 patients with unresectable pancreatic cancer and intractable pain to receive neurolytic celiac plexus block or systemic analgesic therapy alone and reported no impact on survival. In 2011, Wyse *et al.*[4] randomized 96 patients with unresectable pancreatic cancer and related pain to receive endoscopic ultrasound-guided celiac plexus neurolysis at the time of initial diagnosis or conventional pain management and saw no impact on patient survival. In contrast, in the recent report of Levy *et al.*,[5] using endoscopic ultrasound-guidance, 110 patients with unresectable pancreatic adenocarcinoma were randomized to receive celiac plexus neurolysis by depositing alcohol in the area directly surrounding the ganglia with or without combined celiac ganglion neurolysis, where the ganglia were identified and neurolytic solution was placed directly within the ganglia. They hypothesized that direct injection into the ganglia would produce more profound neurolysis and improve outcomes. They found that the opposite was true; the median survival time was significantly shorter for patients receiving the combined celiac plexus/ganglion neurolysis (5.6 months) compared to celiac plexus neurolysis alone (10.5 months) (hazard ratio, 1.49 [95% CI, 1.02 to 2.19]), particularly for patients with non-metastatic disease. They hypothesized that targeted injection of the neurolytic solution might induce local or systemic immune, inflammatory, or metabolic pathways that enhanced tumor growth and spread or that neurolysis negatively impacts other organs and secondarily impacts survival, calling for a reassessment of celiac plexus neurolysis in patients with advanced pancreatic cancer.

There are elements of patient management in this new study[1] that differ from much of the rest of the world and generalizing these findings should be done with caution. The authors tell us, "Patients in palliative care who would not receive any anticancer treatments, including radiation therapy, chemotherapy or targeted therapies." This is extremely unlikely in our own patient population. Most of the patients we see, even with stage IV disease, are receiving some sort of cancer-directed therapies. Indeed, recent advances in treatment have improved patient survival,[7] and current guidelines for treatment of metastatic disease suggest that newer therapies aimed at tumors with specific genetic mutations may have even greater impact.[8] Perhaps there is some interaction between sympathetic neurolysis and such therapies that alters outcomes. In addition, the two most profound positive changes from the block were reduction in pain scores and reduction in opioid doses. The little the authors describe of the opioid dosing regimen suggests that it may have been more conservative than what we would use, and it was entirely restricted to immediate-release morphine and oxycodone (*e.g.*, no long-acting opioids like methadone or transdermal fentanyl). Given that the pain scores became nearly equivalent after several months, it begs the question of whether a more rapid titration of systemic opioids would have eliminated the difference—or at least eliminated the difference more quickly. Furthermore, they infer that more opioids are bad and tell us that there was more constipation and other opioid-related side effects in the systemic therapy alone group but there is no real sense as to whether the increased opioid usage in the systemic therapy group was much of a problem for these patients. When weighing the options for our own patients, the severity of ongoing pain and the presence or absence of bothersome side effects that often accompany high-dose opioid therapy play a major part in the decision to use sympathetic neurolysis.

So, what is the best role for sympathetic neurolysis in the management of pain associated with pancreatic cancer considering the currently available evidence? Two high-quality trials now suggest that neurolysis may reduce survival time after treatment. What is less clear is how neurolysis impacts those with pancreatic cancer at various stages of progression, but the available evidence suggests that there is no impact when a broader group with all stages is treated. Today, practitioners should strongly weigh this new evidence and, perhaps, limit sympathetic neurolysis to those with stage III disease and below, depending on the risks and benefits of each patient's situation and their individual priorities. The evidence also suggests that sympathetic neurolysis might be most effective when performed as early during treatment as possible, rather than waiting for other treatments to fail. Further study will be needed to understand the impact of sympathetic neurolysis in those with more limited disease, but today we should understand what we know about this treatment: sympathetic neurolysis offers reductions in pain and opioid requirements for several months, has no impact on the overall quality of life of those treated, and may reduce survival time after treatment in some patients.

Competing Interests

Dr. Tulsky serves as Chair of the Board of Directors for the Greenwall Foundation, a nonprofit charitable organization located in New York, New York, and has received book royalties from Wolters Kluwer Publishing, Philadelphia, Pennsylvania. The other authors declare no competing interests.

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