Effect of Neurolytic Celiac Plexus Block on Pain Relief, Quality of Life, and Survival in Patients With Unresectable Pancreatic Cancer
A Randomized Controlled Trial

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Pancreatic adenocarcinoma is an aggressive tumor associated with high mortality. Up to 73% of patients are in pain at the time of diagnosis. Thus, a major treatment focus is to optimize the quality of life (QOL) by managing symptoms, especially by providing adequate pain control.

The recommended approach to manage cancer pain uses systemic medications according to the World Health Organization analgesic ladder. At times, systemic analgesics do not provide adequate pain relief, or doses are limited by opioid-related adverse effects. In these circumstances, celiac plexus or splanchnic nerve blocks with neurolytic solutions may provide analgesia by interrupting visceral afferent pain transmission from the upper abdomen.

However, randomized clinical trials evaluating the efficacy of neurolytic celiac plexus block (NCPB) for pancreatic cancer pain have been limited by small sample sizes, lack of blinding, infrequent pain assessments, or lack of standardized delivery of systemic analgesic medications. Indeed, the role of neurolytic blocks in the management of any type of cancer pain has not been firmly established by randomized, blinded clinical trials.

Lillemoe and colleagues showed that patients with unresectable pancreatic cancer randomly assigned to receive in-
traoperative chemical splanchnicectomy during exploratory laparotomy had significantly decreased pain and opioid consumption vs control patients.\textsuperscript{8} In a subgroup of 34 patients with pain before laparotomy, survival was dramatically improved in those receiving chemical splanchnicectomy. Additional data suggest that pain may be associated with decreased survival in pancreatic cancer patients.\textsuperscript{9} Furthermore, it has been shown that animals with implanted tumors have accelerated tumor growth and increased mortality rates when subjected to pain or stress.\textsuperscript{10,11}

Based on these data, we sought to evaluate the possible association of pain and survival in patients with painful pancreatic cancer. The purpose of our prospective, randomized, double-blinded, placebo-controlled clinical trial was to test the hypothesis that NCPB improves pain relief, QOL, and survival vs optimized systemic analgesic therapy (SAT) alone in patients with unresectable pancreatic cancer.

**METHODS**

Following Mayo Institutional Review Board approval, this study was conducted at Mayo Clinic in Rochester, Minn. Patients, 18 years or older, with pancreatic cancer were referred from within the institution to the Mayo Division of Pain Medicine. Patients were of either sex, with the diagnosis of histologically proven or radiologically consistent, surgically unresectable pancreatic adenocarcinoma.\textsuperscript{12} Patients receiving noncurative pancreatic cancer surgery were eligible for study entry beginning at 5 days following their operation. Pain intensity was assessed for each patient using a numerical rating scale (NRS) from 0 to 10 (0 is no pain and 10 is worst pain imaginable).\textsuperscript{13} To enroll, the pain intensity (average in the last 24 hours) rating had to be an NRS of 3/10 or higher and opioid were required for pancreatic cancer-related pain control and an NRS of lower than 6/10 if already optimized on opioids. An optimized opioid therapy was considered the maximum analgesia achievable without intolerable opioid-related adverse effects. Patients were excluded if they had received previous NCPB or other neurolytic blocks that could affect pancreatic cancer-related pain or had implanted epidural or intrathecal analgesic therapy. Patients with psychiatric disease affecting assessments, uncorrectable coagulopathy, or allergy to local anesthetics were excluded.

**Box 1. Modified Stepwise Analgesic Ladder**

**Step 1. Mild to Moderate Pain**
Give patient nonsteroidal anti-inflammatory drug and/or 5 mg of oxycodone with acetaminophen, 500 mg orally (up to 8 tablets/d)

**Step 2. Moderate to Severe Pain**
Give patient sustained-release morphine orally. If the patient cannot tolerate morphine or oral and rectal routes are not possible, give transdermal fentanyl patch or oxycodone sustained-release orally
With additional as-needed morphine immediate release pills or elixir orally or 5 mg of oxycodone with acetaminophen, 500 mg orally (up to 8 tablets/d) for breakthrough pain

**Box 2. Assessments**

**Enrollment**
Basic demographic data (including any prior radiation therapy and/or chemotherapy) were recorded.
The character of the pain, including duration before enrollment, quality, intensity, and location, and its temporal pattern of the pain were obtained.

**Weekly Intervals**
The following data were obtained by the observer by telephone: Pain intensity rating: a verbal description of least, worst, and average pain intensity in the last 24 hours with a numerical rating scale (NRS) ranging from 0 through 10 (0 is no pain and 10 is worst pain imaginable).\textsuperscript{15} Responses to the NRS were obtained directly from the patient as long as circumstances permitted, with proxy responses from spouse or caregiver noted.

**Quality of Life assessments:** The Functional Assessment of Cancer Therapy, Pancreatic Cancer (FACT-PA) is a validated, standardized measurement tool to determine QOL, as an outcome measure, in patients with pancreatic cancer.\textsuperscript{16} Responses to the FACT-PA questions were obtained directly from the patient as long as circumstances permitted, with proxy responses from spouse or caregiver noted.

**Analgesic requirements:** The opioid requirements were converted to daily oral morphine equivalents.\textsuperscript{2,19}

**Adverse effects assessment:** Common opioid-related adverse effects were assessed including nausea, pruritus, constipation, and drowsiness.

**Radiation therapy and/or chemotherapy assessment:** Any use of radiation and/or chemotherapy (gemcitabine, fluorouracil, or other) was recorded.

**Survival time:** These determinations were made from both the date of diagnosis and date of randomization until the date of death.

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(stages III or IV, locally unresectable or metastatic disease, respectively) in blocks of 4 patients to ensure similar numbers in each treatment group. Radiation therapy and chemotherapy were allowed independently. Previous work has shown similar results with different NCPB or splanchnic neurolysis techniques. In this study, patients randomized to NCPB received an alcohol NCPB using a standard needle placement technique. In the prone position, skin and soft tissues of the midback were anesthetized with 1% lidocaine at points located 1 cm below the inferior ribs and 7 cm from the midline on each side. A 22-gauge, 5-inch-long needle was inserted and advanced to the anterolateral aspect of the superior portion of the first lumbar vertebra body on each side. Correct bilateral needle placement was confirmed with negative aspiration and fluoroscopic imaging following injection of 1 to 5 mL of iopamidol (radiocontrast dye). Ten milliliters of 0.5% bupivacaine was injected through each needle. After 10 minutes, a motor and sensory examination of the lower extremities confirmed lack of neurologic deficits. Then, 10 mL of absolute alcohol was injected through each needle.

To control for a placebo response from the NCPB procedure, patients randomized to SAT received a sham procedure using subcutaneous and intramuscular 0.5% bupivacaine injection at typical NCPB sites. This procedure was performed with the identical room and set-up, prone positioning, instruments, fluoroscopy machine movement, personnel, and timing as the actual NCPB. Sham images appeared on the computer screen, but no actual fluoroscopy was used.

Following the randomized procedure, both treatment groups could receive medications according to a modified analgesic regimen based on World Health Organization guidelines (Box 1). When an opioid in combination with a nonopioid analgesic drug (step 1) failed to relieve mild to moderate pain, an appropriate opioid was used to treat severe pain (step 2). These analgesics were dosed in a manner blinded to the patients’ randomized treatment group.

If patients had a 6/10 or higher rating of pain intensity despite optimized opioid medications or experienced intolerable adverse effects to opioid medications, rescue treatment could occur. The rescue consisted of an alcohol NCPB and was performed by a qualified member of the study team, usually the clinical manager, with the initial treatment assignment remaining blinded.

The study team consisted of members with unique roles to maintain the study blinding: the clinical manager was a physician blinded to the randomized intervention who was responsible for all pain management decisions including dosing of analgesic medications; the observer was a clinical research nurse blinded to the randomized intervention who performed all patient assessments (Box 2); the operator was a physician not blinded to the randomized intervention who performed the NCPB or sham procedure. Following the randomized procedure, the operator was not actively involved in the care of that patient. Other medical decisions for each patient were made by the patient’s primary physician.

The number of patients with data available diminished over time due to death, intermittently missed follow-up contacts, and occasional failure to respond to individual follow-up questions. From a repeated measures analysis performed using data from weeks 1 through 24 after randomization, pain intensity was found to decrease gradually with time (P=.002) and was significantly lower for neurolytic celiac plexus block than for systemic analgesic therapy. The numeric rating scale ranges from 0, no pain to 10, the worst pain imaginable.
fined as daily oral morphine equivalents in milligrams), and QOL (Functional Assessment of Cancer Therapy—Pancreatic Cancer [FACT-PA] short form) were collected weekly. The FACT-PA total score was calculated and expressed as a percentage of the maximum possible score, as were the subscale scores for physical well-being, functional well-being, and additional concerns specific to pancreatic cancer. To satisfy model fitting assumptions, opioid consumption was analyzed using a logarithmic transformation \((y = \log_{10}[\text{daily oral morphine equivalents} + 1])\). Data following randomization for these end points were analyzed by repeated measures analysis using general linear models that allow for a varying number of observations and take into account the correlation of data within subjects.50 Study week was included in the model as a regression variable. The treatment \(\times\) study week interaction term was included in initial analyses to evaluate whether the NCPB effect may diminish over time. Given the absence of a significant interaction, subsequent analyses were performed with only main effect terms for treatment and study week. The number of patients with data available diminished over time due to patient death, intermittent missed follow-up contacts, and occasional failure to respond to individual follow-up questions. Due to diminishing sample sizes, data beyond 24 weeks following randomization were not included in any repeated measures analysis. To examine the potential influence of missing data, analyses were repeated with intermittent missing data imputed using linear interpolation and missing data due to patient death imputed using the last observed data value. The percentage of patients’ rating a given opioid based on adverse effect as moderate or any time during the first 6 weeks following randomization was compared between treatment groups using the Fisher exact test. Time-to-rescue therapy was compared between groups using the log-rank test. In all cases, 2-sided tests were used with \(P \leq .05\) considered statistically significant. All analyses were performed using SAS statistical software (Version 8.2 of the SAS System for Unix, SAS Institute Inc, Cary, NC).

RESULTS

Between October 1997 and January 2001, 173 patients were screened for enrollment (Figure 1). Of these, 153 (88%) met study inclusion criteria and 20 were excluded. Of the 153 eligible study patients, 101 (66%) agreed to participate. One patient was withdrawn because the diagnosis changed from pancreatic adenocarcinoma to a less aggressive tumor. The remaining 100 patients were followed up weekly for at least a year (through March 2002) or until their death, forming the study cohort. To evaluate for the possible presence of inclusion biases, we reviewed available medical records of patients who met study inclusion criteria for variables including age, sex, presence of significant pain or requirement of opioid use for pain, and disease stage. In all cases, there were no significant differences for those enrolled in the study vs those not enrolled using a 2-sample t test or \(\chi^2\) test, as appropriate.

At enrollment, the treatment groups had similar treatment history: radiation therapy (16% NCPB vs 10% SAT, \(P = .37\)) or chemotherapy (22% NCPB vs 18% SAT, \(P = .62\)) for any chemotherapy [gemcitabine, fluorouracil, or other] or 6% NCPB vs 8% SAT, \(P = .70\) for gemcitabine). During the first 6 weeks following randomization, 8 patients (16%) in each treatment group received radiation treatment. During this initial 6-week period, the percentage of patients who received some form of chemotherapy was similar between treatment groups (60% NCPB vs 56% SAT, \(P = .69\)) as was the percentage of patients who received gemcitabine (46% NCPB vs 38% SAT, \(P = .42\)). Since the possible use and timing of radiation therapy and/or chemotherapy were not controlled for in our study cohort, further analyses evaluating their potential effects would be subject to bias and were therefore not performed.

Baseline characteristics were similar between groups (Table 1). Seventy-eight percent of patients reported constant abdominal pain and 47% reported constant back pain. There were no significant mean (SD) differences in baseline pain intensity (4.4 [1.7] NCPB vs 4.1 [1.8] SAT, \(P = .41\)), QOL (50.5 [15.0] NCPB vs 51.2 [16.1] SAT, percentage of maximum FACT-PA total score, \(P = .82\)), or the percentage of patients using opioid medications (26% NCPB vs 42% SAT, \(P = .09\)).

At week 1, the mean pain intensity significantly decreased for each group from baseline. For the NCPB group, the mean (SD) pain intensity at week 1 in-

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NCPB, neurolytic celiac plexus block; NRS, numerical rating scale; SAT, systemic analgesic therapy.

**Table 2. Pain Intensity and Quality of Life**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>SAT</th>
<th>NCPB</th>
</tr>
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<tbody>
<tr>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Pain, 1-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>1.0 (1.7)</td>
<td>4.2 (3-5)</td>
</tr>
<tr>
<td><strong>Week 1</strong></td>
<td>2.7 (2.1)</td>
<td>3 (1-3.4)</td>
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<td></td>
<td>2.5 (1.6)</td>
<td>2 (1-3.4)</td>
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<tr>
<td></td>
<td>1.8 (1.7)</td>
<td>1 (0-3)</td>
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<td>2.0 (1.5)</td>
<td>2 (1-3.5)</td>
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<td></td>
<td>1.7 (1.5)</td>
<td>2 (0-3)</td>
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<td>2.4 (2.4)</td>
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<tr>
<td></td>
<td>2.0 (2.2)</td>
<td>1 (0-3)</td>
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</tbody>
</table>

**Quality of Life†**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>SAT</th>
<th>NCPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>51.2 (16.1)</td>
<td>51.1 (38.0-63.0)</td>
</tr>
<tr>
<td><strong>Week 1</strong></td>
<td>64.2 (17.1)</td>
<td>64.1 (49.3-76.6)</td>
</tr>
<tr>
<td></td>
<td>63.6 (16.2)</td>
<td>60.3 (51.6-77.2)</td>
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<tr>
<td></td>
<td>61.6 (18.8)</td>
<td>61.4 (42.7-78.0)</td>
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<tr>
<td></td>
<td>60.9 (17.5)</td>
<td>57.1 (47.3-73.1)</td>
</tr>
<tr>
<td></td>
<td>62.1 (18.6)</td>
<td>62.9 (49.0-75.0)</td>
</tr>
<tr>
<td></td>
<td>62.7 (18.2)</td>
<td>60.6 (49.5-76.1)</td>
</tr>
<tr>
<td></td>
<td>59.7 (25.5)</td>
<td>54.8 (42.5-88.9)</td>
</tr>
</tbody>
</table>

**Abbreviations:** IQR, interquartile range; NCPB, neurolytic celiac plexus block; SAT, systemic analgesic therapy.

*Patients were followed up weekly until death. Data are presented for selected weeks. Declining sample sizes for the observed data reflect attrition due to patient death, intermittent missed follow-up contacts, and occasional failure to respond to individual follow-up questions. For the carry-forward technique, missing data due to patient death are imputed using the last observed data value and intermittent missing data are imputed using linear interpolation. Using this approach, 50 patients were used for both groups at all periods with the exception of quality of life for patients in the NCPB group, for which 49 patients were used for each period.

†Quality of life was assessed using the Functional Assessment of Cancer Therapy Scale for Pancreatic Cancer (FACT-PA). Data represent the FACT-PA total score expressed as a percentage of the maximum possible score.

Opioid consumption increased with time (β=0.06, SE=0.005, P<0.002, analyzed using log10 transformation) with no evidence of a difference between groups (β=−0.01, SE=0.141, P=0.93). During the first 6 weeks after randomization, the percentage of patients reporting moderate or severe opioid adverse effects did not differ significantly between treatment groups (nausea 50% vs 38%, pruritus 16% vs 10%, sedation 46% vs 30%, and constipation 40% vs 52% for NCPB vs SAT; P=0.10 for all, Table 3).

Following week 1, QOL (FACT-PA total score) gradually declined with time (β=−0.35, SE=0.15, P=0.02) and did not differ between groups (β=−2.11, SE=2.81, P=0.46). The physical and functional well-being subscales of the FACT-PA each decreased with time (physical β=−0.67, SE=0.24, P<0.002; functional β=−0.51, SE=0.24, P<0.001) with no evidence of a difference between groups (physical β=−0.35, SE=0.15, P=0.02, functional β=−0.41, SE=0.15, P=0.02). During the first 6 weeks after randomization, no significant difference was observed between treatment groups (physical β=−0.01, SE=0.141, P=0.93, functional β=0.00, SE=0.141, P=0.93).

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functional $\beta = -0.66, SE = 0.24, P = 0.008$ with no difference between groups (physical $\beta = -1.44, SE = 3.30, P = 0.21$; functional $\beta = -3.42, SE = 4.06, P = 0.40$; Table 2). The additional subscale for concerns specific to pancreatic cancer did not change significantly over time ($\beta = 0.09, SE = 0.17, P = 0.59$) and did not differ between groups ($\beta = 1.36, SE = 2.48, P = 0.59$). An additional analysis was performed for the FACT-PA item that asks patients to rate the truth of the statement, “I have pain” using the following responses: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; or 4, very much. From this analysis, pain was found to decrease gradually with time ($P = 0.003$) and was significantly lower for the NCPB than for the SAT group ($P = 0.02$). A total of 13 patients (3 NCPB, 10 SAT) received rescue NCPB for pain relief following randomization. Time to rescue was significantly longer for those in the NCPB than for those in SAT groups ($P = 0.01$, log-rank test; Figure 3). In all cases, similar findings were obtained when the analyses of pain intensity, opioid consumption, and QOL were repeated using only data collected prior to rescue. Findings were also consistent when intermittent missing data were imputed using linear interpolation and missing data due to patient death imputed using the last observed data value.

At the time of last follow-up, 96 (47 NCPB, 49 SAT) patients were deceased. Survival following randomization did not differ significantly between treatment groups ($P = 0.26$; hazard ratio, 0.8; 95% confidence interval [CI], 0.5-1.2; proportional hazards regression adjusting for stage of disease; Figure 4). Median survival for patients with stage III disease was 5.5 months for NCPB and 6.1 months for SAT. For patients with stage IV disease, the median survival was 2.9 months for NCPB and 3.4 months for SAT. The percentage of patients alive a year after randomization was 16% (12% stage III, 18% stage IV) for NCPB patients and 6% (6% stage III, 6% stage IV) for SAT patients.

**COMMENT**

A recent National Institutes of Health State-of-the-Science Conference Statement on Symptom Management in Cancer (July 15-17, 2002) highlighted the lack of properly designed comparative analgesic trials for cancer patients such as NCPB vs SAT in the
CELIAC PLEXUS BLOCK FOR PANCREATIC CANCER PAIN

Figure 4. Survival After Randomization by Cancer Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. at Risk</th>
<th>Month After Randomization</th>
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</thead>
<tbody>
<tr>
<td>III</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>4</td>
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<tr>
<td>IV</td>
<td>17</td>
<td>5</td>
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<tr>
<td></td>
<td>8</td>
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<td>9</td>
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<td></td>
<td>2</td>
<td>10</td>
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</tbody>
</table>

Survival after randomization did not differ significantly between treatment groups (P = .26); proportional hazards regression adjusting for stage of disease.

Our major finding is that NCPB significantly improves pain relief in patients with pancreatic cancer compared with optimized SAT alone but does not affect QOL or survival.

Both NCPB and SAT were able to provide a clinically meaningful reduction in pain intensity from baseline, which is similar to previous findings.5,7 Opioid therapy was implemented or intensified in both groups. During the first week after intervention, NCPB provided analgesia with a mean pain rating similar to other studies,5,6 which was significantly better than SAT alone, demonstrating that our block technique was effective. Furthermore, the analgesic benefit of NCPB over SAT alone was sustained over the longer term until death. This finding is similar to the larger study of chemical splanchnicectomy during surgery (n=137) by Lillemoe et al8 but different from previous smaller unblinded studies (20 to 24 total patients) primarily showing short-term analgesic benefit over weeks with NCPB compared with SAT.5,7 The efficacy of the NCPB is also suggested by our finding that more patients randomly assigned to SAT required NCPB rescue (Figure 3).

A previous study found that up to 85% of patients with advanced pancreatic cancer experience severe pain with advanced disease.23 Our results suggest that application of a pain management protocol, with or without NCPB, can maintain pain intensity in the “mild”21 category over time in most patients, even those with advanced disease. Our interpretation is that NCPB is an efficacious adjunctive analgesic therapy, but a key intervention is the implementation of an aggressive pain management protocol with opioids used throughout the course of disease. It is possible that the treatment effect size provided by the NCPB would have been larger if the SAT were not as optimized, as might occur in certain clinical practice settings.

In clinical practice, opioid doses required for adequate analgesia in cancer patients, even among those with similar tumors, are extremely variable as observed in our study. Opioids were frequently required even in those receiving NCPB, as previously observed by Ischia et al,14 with no difference between groups. This result is different from the findings of Lillemoe et al,8 which did not control for delivery of opioids according to need, approach, or provider. Other smaller studies5,7 of between 20 and 24 patients were not double blinded, thereby, potentially biasing those not receiving the active treatment with NCPB to requiring increased opioids.16

At week 1, QOL improved as pain relief improved but without difference between groups. As expected, QOL estimated by the FACT-PA declined over time but without difference between groups. A previous small study showed decreased deterioration of QOL estimated by functional status in those with NCPB.5 It is possible that the relatively smaller difference in pain scores between groups in our study was insufficient to affect the more global assessment of QOL estimated by the FACT-PA.

We sought to further evaluate the possible association between pain and survival. A higher percentage of patients were alive a year after randomization to NCPB (16%, n=8) vs SAT (6%, n=3), but this difference was not significant. Lillemoe et al had a different finding with improvement in survival and in pain relief, but only in a small subgroup with significant preoperative pain (≥3/10) randomly assigned to receive chemical splanchnicectomy (n=20) vs controls (n=14). Compared with our study, there are distinct differences in the Lillemoe et al study including a different celiac block technique using chemical splanchnicectomy during surgery, a different study population consisting entirely of surgically operated patients, a relatively small sample size when considering only patients with significant pain (n=34), much less frequent pain assessments occurring every 2 months, and lack of a standardized approach to providing analgesic therapy that would be difficult to optimize. Also, the pain ratings in the study by Lillemoe et al were higher in both chemical splanchnicectomy and controls with larger absolute

management of pancreatic cancer pain.
mean differences between groups compared with our study at similar time points. It is possible these factors may have contributed to the difference in findings between the Lillemeoe et al study and our study. Furthermore, although the current investigation was designed to provide 90% power to detect a difference in survival based on the results of Lillemeoe et al (ie, doubling of survival for NCPB vs SAT), the sample size for the current investigation may not provide adequate statistical power to make definitive conclusions regarding smaller differences in survival that still may be clinically relevant.

In conclusion, we found that both NCPB and optimized SAT alone can provide effective analgesia, though NCPB can provide significantly better analgesia than optimized SAT alone. However, the NCPB had no effect on opioid consumption, QOL, or survival.

Author Contributions: Dr Wong had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wong, Schroeder, Warner. Acquisition of data: Wong, Carms, Wilson, Martin, Kinney, Mantilla. Analysis and interpretation of data: Wong, Schroeder, Warner.

Drafting of the manuscript: Wong, Schroeder, Warner. Critical revision of the manuscript for important intellectual content: Wong, Schroeder, Carms, Wilson, Martin, Kinney, Mantilla, Warner. Statistical expertise: Wong, Schroeder. Obtained funding: Wong, Warner. Administrative, technical or material support: Wong, Carms, Martin, Kinney, Mantilla.

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REFERENCES