Randomized Controlled Trial of Epidural-General Anesthesia versus General Anesthesia for Open Pancreaticoduodenectomy: Influence on Complications and Overall Two Year Survival

PROTOCOL FACE PAGE FOR MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites
Manhattan
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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title: Randomized Controlled Trial of Epidural-General Anesthesia versus General Anesthesia for Patients Undergoing Pancreaticoduodenectomy: Effects on Complications and Overall Two Year Survival

Objectives: To determine if an intraoperative Epidural-General Anesthesia Technique plus post-operative epidural analgesia (EG) compared with an intraoperative General Anesthesia Technique with post-operative epidural analgesia (GA):

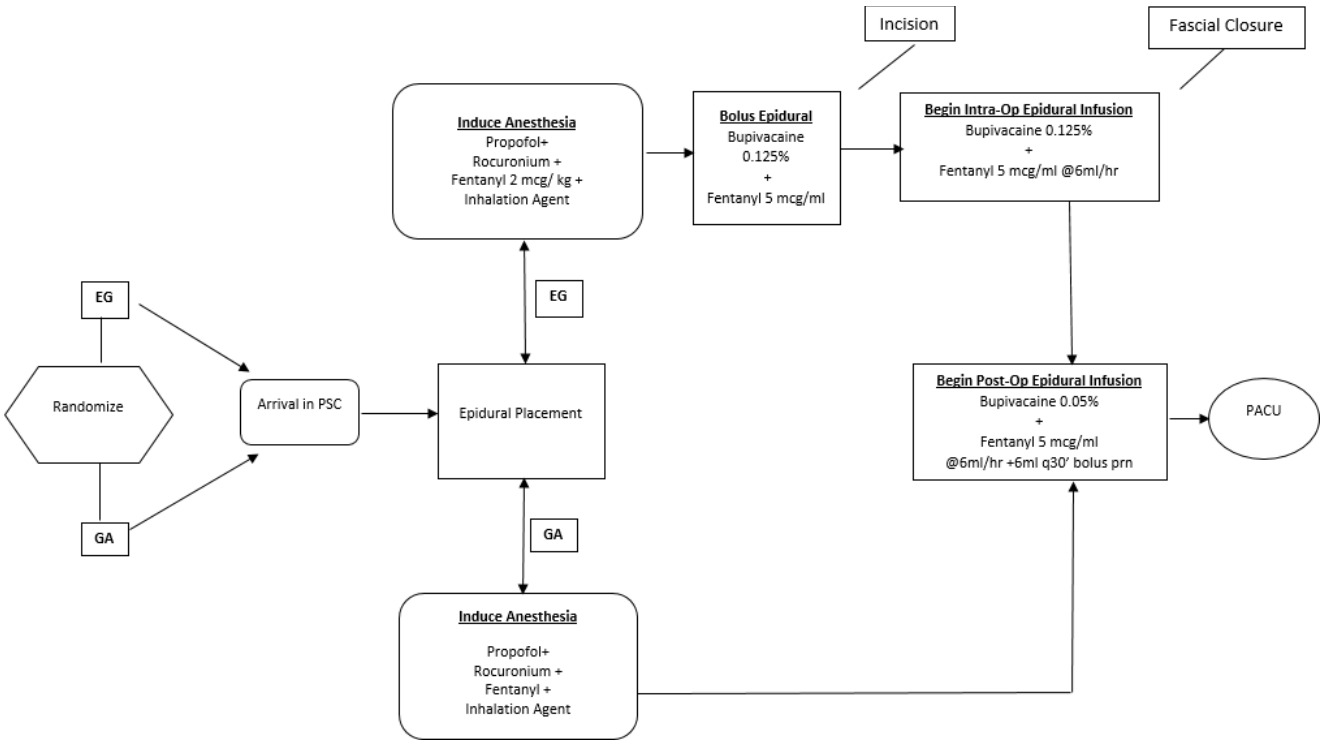
1) results in fewer Grade 3 or greater post-operative complications as described at https://one.mskcc.org/sites/pub/surgery/Pages/Secondary-Events.aspx and based on the Dindo, Clavien grading system. [1-4]
2) results in prolonged survival at 2 years in patients with adenocarcinoma,
3) decreases patient length of stay (LOS),
4) decreases post operative delirium.

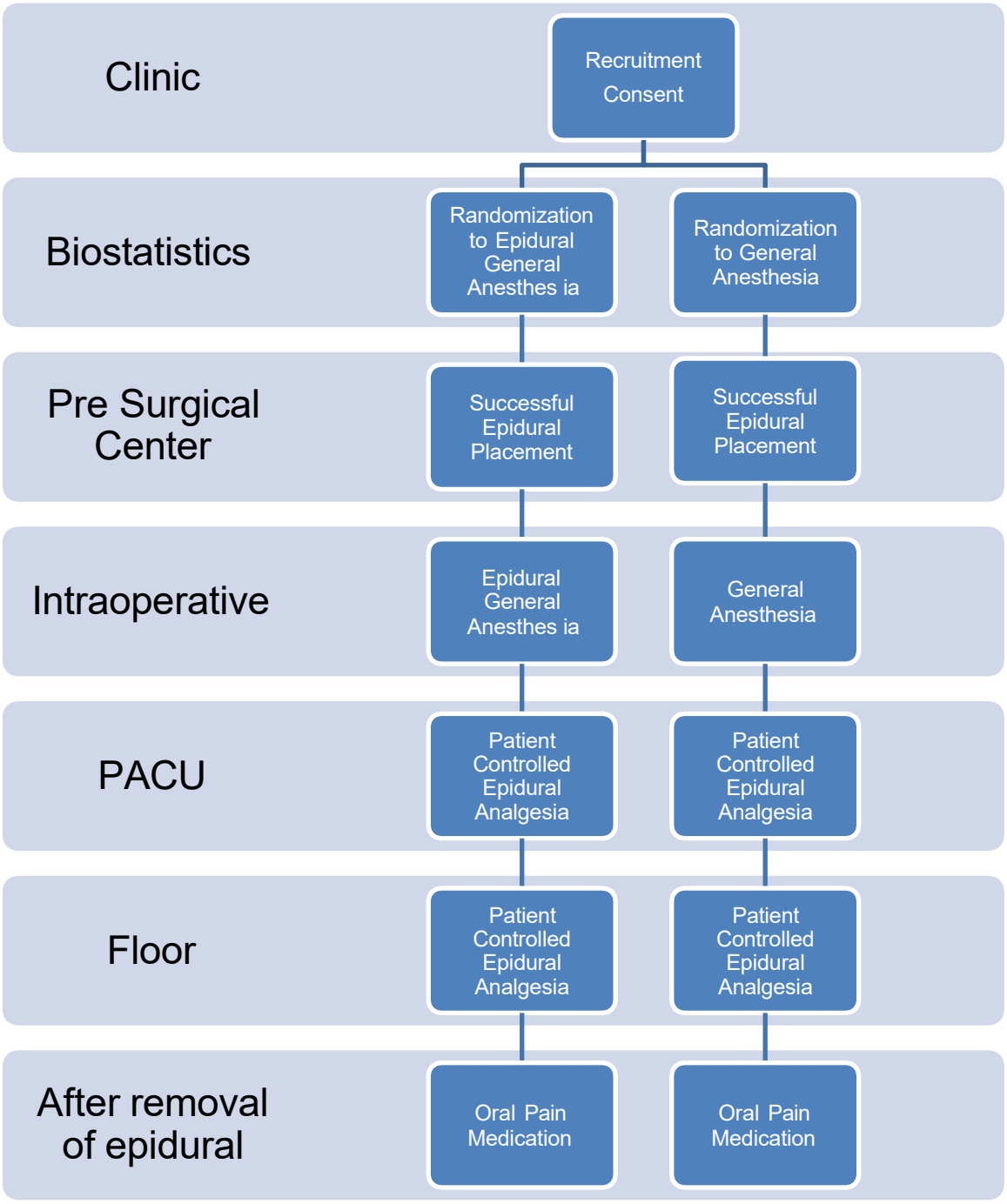
Patient Population: Adult patients ≥ 18 years old who are scheduled for pancreaticoduodenectomy at MSKCC.

Design: Prospective randomized controlled single institution trial.

Treatment Plan: Patients will be consented to the study in the surgical or pre-anesthesia clinics and then randomized in the Pre-Surgical Center after successful epidural placement to receive either an intraoperative Epidural-General Anesthetic Technique plus post-operative epidural analgesia (EG) or a General Anesthetic Technique with post-operative epidural analgesia (GA).

Time to Completion: Estimated time to completion is 3 to 4 years.


Incision
Fascial Closure
Induce Anesthesia
Propofol+
Rocuronium +
Fentanyl 2 mcg/ kg +
Inhalation Agent
Bolus Epidural
Bupivacaine
0.125%
+
Fentanyl 5 mcg/ml
Begin Intra-Op Epidural Infusion
Bupivacaine 0.125%
+
Fentanyl 5 mcg/ml @6ml/hr
EG
EG
Randomize
Arrival in PSC
Epidural Placement
Begin Post-Op Epidural Infusion
Bupivacaine 0.05%
+
Fentanyl 5 mcg/ml
@6ml/hr +6ml q30' bolus prn
PACU
GA
GA
Induce Anesthesia
Propofol+
Rocuronium +
Fentanyl +
Inhalation Agent



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary:

- To determine if intraoperative Epidural-General anesthesia plus post-operative epidural analgesia (EG) decreases the incidence of Grade 3 or greater complications (See Appendix 1 and described above) in adult patients undergoing

pancreaticoduodenectomy (PD), as compared to General Anesthesia with epidural for post op analgesia (GA).

Secondary:

- To determine if EG improves 2-year survival in adult patients undergoing pancreaticoduodenectomy (PD) for adenocarcinoma as compared to GA.
- To determine if EG results in decreased LOS in patients undergoing pancreaticoduodenectomy as compared to GA.

Exploratory:

- To determine if EG decreases the incidence of post operative delirium as compared to GA.

3.0 BACKGROUND AND RATIONALE

Pancreatic cancer is one of the deadliest cancers. In 2016, it moved from the fourth to the third leading cause of cancer-related death in the U.S., surpassing breast cancer. Pancreatic cancer is the 11th most commonly diagnosed cancer in men and the ninth in women. While overall cancer incidence and death rates are declining, the incidence and death rates for pancreatic cancer are increasing. The vast majority of pancreatic cancer cases are diagnosed after they have spread.

Over 70% of patients will die within the first year of diagnosis. While surgery offers the best chance for survival, fewer than 20 percent of pancreatic cancer cases are diagnosed early enough for surgical intervention. For all stages of pancreatic cancer, patients have a one year survival of 20% and a five year survival of 7%, depending on a balance between the histology and metastatic potential of the tumor, the stage when it is diagnosed, the completeness of the resection and the competency of the immune system of the host in the defense against metastases.[5] Even with surgery, the eventual prognosis is poor with a median survival of roughly 18 months. The overall five-year survival rate is about 10%, although this can rise as high as 20% to 35% if the tumor is removed completely and when cancer has not spread to lymph nodes. In a recent prospective analysis we found a survival rate of 88% at one year and 80% at 2 years after successful surgical resection.[6]

Complications after surgery affect survival

The surgery itself carries a high morbidity with a major complication rate upwards of 30% in most institutions. We have recently reported a rate of Grade 3 (see Appendix 1) or greater complications of 27% in 218 pancreaticoduodenectomies performed in a high volume center.[6] In addition, we reviewed both our published data of 1030 cases from 2004 – 2009[7] as well as the resection database at our institution for the past 5 years and found in 1028 pancreaticoduodenectomies Grade 3 complication rates of 35 and 33% overall. (MSK internal communication). Major post-operative complications, particularly infectious

complications, are associated with impaired long-term survival.[8-15] The most common complications after pancreatectomy are intraabdominal fluid collections/abscesses and pancreatic leaks/fistulae, making up approximately 25% of all complication. [6,7]

Epidurals may decrease post-operative complications

Benefits of epidural use peri-operatively have previously been demonstrated in reviews of the literature, including lower complication rates, earlier return to bowel function, reduced blood loss and decreased LOS.[16,17] The hypothesis is that epidural anesthesia and analgesia (EAA) can improve surgical outcome by reducing postoperative morbidity and hastening recovery. Likely benefits include decreased incidence of cardiac complications in high-risk patients; lower incidence of pulmonary complications, lower incidence of DVT and pulmonary embolus; suppression of the neuroendocrine stress response; and earlier return of gastrointestinal function. [16] There is a positive association between epidural as the primary anesthetic and decreased post-operative complications in various operative procedures.[17]

A large literature review of retrospective, prospective, and meta-analysis studies has demonstrated an improvement in surgical outcome through beneficial effects on perioperative pulmonary function, blunting the surgical stress response and improved analgesia. In particular, significant reduction in perioperative cardiac morbidity (approximately 30%), pulmonary infections (approximately 40%), pulmonary embolism (approximately 50%), ileus (approximately 2 days), acute renal failure (approximately 30%), and blood loss (approximately 30%) were noted in one groups review of the literature.[17]

In the MASTER Trial,[18] adverse outcomes in high-risk patients managed for major surgery with epidural block or alternative analgesic regimens with general anesthesia were compared in a multicenter randomized trial. In this trial, 915 patients undergoing major abdominal surgery with high-risk status were randomly assigned intraoperative epidural anesthesia and postoperative epidural analgesia for 72 h with general anesthesia or control. The primary endpoint was death at 30 days or major postsurgical morbidity. They found that most adverse morbid outcomes were not reduced by use of combined epidural and general anesthesia and postoperative epidural analgesia. However, the improvement in analgesia, reduction in respiratory failure, and the low risk of serious adverse consequences suggested that many high-risk patients undergoing major intraabdominal surgery would receive substantial benefit from combined general and epidural anesthesia intraoperatively with continuing postoperative epidural analgesia.[19]

A review by Fotiadis found that epidural analgesia is associated with a shorter duration of postoperative ileus, attenuation of the stress response, fewer pulmonary complications, and improved postoperative pain control and recovery. It does not reduce anastomotic leakage, intraoperative blood loss, transfusion requirement, risk of thromboembolism or cardiac morbidity, or hospital stay compared with that after conventional analgesia in unselected patients undergoing gastrointestinal surgery. They concluded that thoracic epidural analgesia reduces hospital costs and stay in patients at high risk of cardiac or pulmonary complications.[20]

A review by Holte found no statistically significant evidence from randomized trials to indicate epidural analgesia with local anesthetic to be associated with an increased risk of anastomotic breakdown in colorectal surgery. However, relatively few patients have been included in randomized trials.[21]

In a randomized trial of patients aged 70 or greater undergoing major abdominal surgery, where one group received EG and the other GA with post operative intravenous analgesia, the EG group had better pain relief and improved mental status on POD 4 and 5, but no difference in delirium.[22]

There have been mixed results when epidurals are utilized in patient undergoing **pancreaticoduodenectomy**. Epidurals for post op analgesia after pancreaticoduodenectomy have been associated with lower pain scores, but may also increase complications including pancreatic fistulae, post-operative ileus, LOS, increased transfusion requirements, aggressive fluid resuscitation and higher rates of gastrointestinal and respiratory complications.

Pratt's group evaluated data for 233 consecutive patients, who underwent pancreaticoduodenectomy, were prospectively acquired and retrospectively reviewed. One hundred eighty-five patients received epidural **analgesia**, and 48 received intravenous analgesia. Patients administered epidural analgesia had lower pain scores but significantly higher rates of major complications. Pancreatic fistulae and postoperative ileus occurred more frequently, and patients with epidural analgesia more often required discharge to rehabilitation facilities. Thirty one percent of epidural infusions were aborted before anticipated (fourth postoperative day) because of hemodynamic compromise and/or inadequate analgesia. These select patients required more transfusions, aggressive fluid resuscitation, and subsequently suffered even higher rates of gastrointestinal and respiratory complications, all attributing to higher costs. [23]

However, in some more recent studies, epidural **analgesia** is associated with lower post-operative complications following pancreaticoduodenectomy.[24] A large review of pancreatectomies utilizing the Nationwide Inpatient Sample showed those patients who received epidurals had decreased LOS, hospital charges, respiratory failure/pneumonia and inpatient mortality.[25] Another retrospective review found fewer incidences of sepsis, post-operative hemorrhage, liver failure, post-operative pneumonia and respiratory failure as well as lower in-hospital mortality.[26]

To date there are rare randomized controlled trials in patients undergoing pancreatic resection utilizing epidurals at anesthetic levels, and all except one study mentioned are retrospective. Control for epidural local anesthetic concentrations, infusion rates and timing of administration were not made in the retrospective reviews. Based on methods published, determination of intraoperative epidural anesthesia versus postoperative utilization of epidural analgesia is lacking. Two studies addressed timing of epidural administration and standardization of local anesthetic concentrations and rates.[23,27] The study which prospectively accrued was not randomized and created an imbalance between the epidural (n=185) versus no epidural (n=48) group.[17,23] While the authors addressed timing of epidural

administration and utilized standardized local anesthetic concentrations and rates, they had a high epidural failure rate (31%) and intraoperative IV opioids were used. The other study with standardized infusion rates did not start the epidural until the start of skin closure.[27]Lack of consistency in local anesthetic concentrations and time to initiate epidural infusions provide conflicting data for anesthetic management in patients undergoing pancreatic resection, and it remains unclear if epidural analgesia provides additional benefits to this patient population.

A very recent randomized trial comparing thoracic epidural analgesia with epi general anesthesia to intravenous patient-controlled analgesia for pain control over the first 48 hours after hepatopancreatobiliary surgery (4 pancreas resections) found no increased length of stay or complications.[28] We propose to ascertain whether intraoperative epidural anesthesia has any effect on postoperative complications.

Surgery and Anesthesia affect immunity, which affects survival

It is long known that peri-operative immune suppression can be caused by surgical stress and anesthesia.[29] Natural killer (NK) cells, a subpopulation of lymphocytes, are the body's primary defense.[30] They recognize and destroy virally infected and tumor cells during the metastatic process.[31] There is evidence that stress-induced decrease in NK cells can enhance tumor development.[32] This decrease can last for up to 30 days after surgery.[33-35]

Surgical resection, the mainstay of treatment for early stage pancreatic cancer, suppresses cellular immunity for several days, peaking at day 3[5,36] and displays a direct toxic effect on NK cells.[37,38] Studies in humans have shown that surgery itself can promote the development of metastases by inhibiting (NK) cell activity, [32] which has been associated with increased mortality and cancer recurrence.[39-42]

Activation of the neuroendocrine system in response to surgery causes increased production of adrenocorticotropic hormone (ACTH) from the pituitary gland and release of glucocorticoids from the adrenals, also causing suppression of cell-mediated immunity.[43,44] Cortisol decreases proliferation of T lymphocytes.[45] The lymphocyte population decrease perioperatively is proportional to the magnitude of the surgery.[29,33-35,46-48] The release of catecholamines from activation of the sympathetic nervous system also has immunosuppressive effects.[49]

General anesthesia. NK cell activity increases following anesthetic pre-medication and during induction, followed by a decrease post-operatively,[33-35] [50] [51] as well as impairing other immune function.[52] Ketamine and thiopental, but not propofol or diazepam, increase viable tumor cells in the lungs of rats and decrease NK cell activity.[52] Propofol has also been shown to have less of a negative effect on circulating lymphocytes than other anesthetic agents.[53] Isoflurane inhibits Interferon (IFN) stimulation of NK cells in mice,[54] where sevoflurane alters the release of cytokines *in vitro* by NK cells.[55]

Opioids have been shown to suppress both cell-mediated and humoral immunity,[56-63] including post-operative NK cell cytotoxicity,[64,65] which may enhance metastasis and tumor recurrence.[66] The effect may be dose dependent.[64] They may also increase angiogenesis

and promote tumor neovascularization.[57] However, they also relieve surgical stress which may enhance immunity.[67,68] Morphine used in analgesic doses may reduce the tumor promoting effects of surgery.[69]

Some anesthetic techniques may enhance immunity

Local anesthetics may have an antitumor effect.[70] General anesthesia combined with local anesthesia may be able to reduce metastasis and recurrence after surgery.[71] [39-42,72] Patients who received an epidural-general technique intraoperatively showed dominance in T-helper cells and a decline of immunosuppressive T cells after surgery in patients with liver cancer[73] and in patients undergoing thoracotomy.[74] In patients undergoing radical resection for cervical and ovarian cancers, those who received an EG technique had less suppression of NK cell activity, higher levels of the antitumorigenic cytokines and lower levels of the protumorigenic cytokines post-operatively. This immune suppression may last up to two weeks post-operatively.[29] In a study of patients undergoing major intraabdominal surgery, those who received an intra-operative EG technique showed lower levels of epinephrine and cortisol intra-operatively. Lymphocytes and T-helper cells were also higher in the epidural group on POD1.[75] In colon cancer surgery, studies have shown that the epi-general group had significantly greater numbers of lymphocytes and Th1 cells and lower Th2 and regulatory T cells post surgery[76], as well as decreased levels of CRP [77]. This study also showed a decreased time to return of bowel function and full diet.[77] In surgery for gastric cancer, EA has also been shown to lower the stress reaction and decrease the impact on immune function.[78,79] Regional anesthesia may have an effect on cancer recurrence by attenuating the immunosuppressive effects of surgery and decreasing the stress response [80] [81] Regional anesthesia may be associated with improved overall survival after oncologic surgery but the data does not support reduced cancer recurrence.[18,19,82-86]

In a small study in patients who underwent optimal surgical debulking for ovarian cancer, **intraoperative use** of epidural anesthesia was associated with an increased time to tumor recurrence after surgery. The intraoperative use epidural group had a mean (95% confidence interval) time to recurrence of 73 (56-91) months, which was longer than either the epidural postoperative group 33 (21-45) months (P = 0.002) or the no-epidural group 38 (30-47) months (P = 0.001). The postoperative-only and no-epidural groups were not different (P = 0.92). Intraoperative epidural significantly reduced (hazard ratio, 0.37 [95% confidence interval, 0.19-0.73]) tumor recurrence risk.[72] Another trial investigating immune function in women with epithelial ovarian cancer undergoing radical resection with either general anesthesia alone or in combination with epidural anesthesia found that combined general/epidural anesthesia appeared to promote antitumorigenic responses.[87]

In a retrospective review of patients with invasive prostatic carcinoma who underwent open radical prostatectomy and had either general anesthesia-epidural analgesia or general anesthesia-opioid analgesia, after adjusting for several tumor variables, the epidural plus general anesthesia group had an estimated 57% (95% confidence interval, 17-78%) lower risk of recurrence compared with the general anesthesia plus opioids group, with a

corresponding hazard ratio of 0.43 (95% confidence interval, 0.22-0.83; P = 0.012). They concluded that open prostatectomy surgery with general anesthesia, substituting epidural analgesia for postoperative opioids, was associated with substantially less risk of biochemical cancer recurrence.[30]

In a retrospective review of patients undergoing colorectal cancer surgery, the authors found that the use of epidural analgesia for perioperative pain control was not associated with a decreased cancer recurrence, in contrast to other studies; however, a potential benefit was observed in older patients. The benefit of regional anesthesia on cancer recurrence may depend on the specific tumor type.[88]

A retrospective study in patients with **pancreatic** cancer aimed to assess associations between perioperative management and survival in patients undergoing resection. Survival data and anesthetic records for 144 patients who had surgical resection of pancreatic adenocarcinoma were obtained and associations were sought between survival and 19 predefined variables. The authors found increased survival in patients who received perioperative epidural analgesia. An association between use of epidural anesthesia during primary pancreatic cancer surgery and prolonged survival was also observed.[89]

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis by inhibiting the cyclooxygenase enzyme. Tumor cells secrete prostaglandins which may allow them to potentially be targeted by the use of NSAIDs which may be effective in restoring immune competence,[65] preventing cell proliferation, apoptosis and/or angiogenesis.[90] NSAIDs also reduce prostaglandin E2 induced immunosuppression.[91]

Post-operative pain has also been shown to facilitate cancer metastases.[57,69]

Since the complication rate after PD is so high and survival is so low, anything we as anesthesia providers can do to mitigate either would be valuable to this patient population. By decreasing postoperative complications and providing an immunosupportive perioperative course (mitigating the immunosuppressive effects of anesthesia and surgery), we may be able to affect survival as well as length of stay in hospital. We can achieve this by using techniques which decrease complications as well as minimize the neuroendocrine and cellular stress responses associated with surgery and maintain adequate pain control. We believe that adding an intra-operative epidural anesthetic technique while minimizing the use of agents associated with immunosuppression and potentially decreasing post-operative surgical complications may affect the outcome of patients undergoing surgical resection for pancreaticoduodenectomy.

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Finally we will compare the incidence of delirium postoperatively in patients in each arm due to the high incidence of delirium found in cancer patients in hospital, increasing healthcare costs, length of stay, long term cognitive decline and mortality. [92-94] At MSK in patients undergoing major surgery, patients with delirium had a longer length of stay and a greater likelihood of discharge to a rehabilitation facility.[95,96]

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This will be a prospective randomized assessor (surgical staff) blinded controlled study. Since the interventional arm will be receiving a continuous epidural infusion, it would not be possible to blind the anesthesia care provider for the intervention. Additionally, once surgical incision is made, the provider would be able to determine which patient's epidural was injected with placebo as the patient response to incision would be much greater than those patients receiving local anesthetic prior to incision.

Postoperatively, the complication data points will be collected by nursing and surgical staff. The treatment arm information is not available to those doing the assessments. As all patients will have epidurals postoperatively and the treatment from then on is the same, it will not be obvious which treatment arm the patient is on.

Eligible patients will be consented for the trial in the Hepatopancreaticobiliary or Pre-Anesthesia clinic before surgery. Prior to the insertion of epidural catheter at the Pre-Surgical Center which occurs on the day of surgery, patients will be randomized by the Research staff to either an EG anesthesia technique plus post-operative epidural analgesia or a standard GA with post-operative epidural analgesia the day before surgery using CRDB.

Pre-operative: preparation and instruction standard for all patients:

NPO past midnight except for clear liquids up to 2 hours before arrival to the hospital, including medications.

Baseline weight and vital signs pre-operatively including mean arterial pressure (MAP).

An intravenous catheter (IV) will be placed in the Pre-Surgical Center.

An epidural catheter will be placed as per usual clinical practice by a member of the anesthesia pain service or the attending anesthesiologist as described in section 9.0

Intra-operative Management: Standard and common to *both* arms. Specifics to Intervention Arm described in Section 4.2 below.

- All patients will be transported to the OR and secured onto the operative table after appropriate identification.
- Routine monitors will be placed per usual clinical practice, in addition to the Bispectral Index (BIS) or other cerebral monitor, which will be maintained intraoperatively between 40-60 per manufacturer's guidelines.

- After pre-oxygenation, general anesthesia will be induced in a standard fashion with propofol, rocuronium or vecuronium and fentanyl. The intervention group will receive no more than 2mcg/kg of fentanyl IV for induction.
- All patients will receive acetaminophen 1G IV q 8 hours for 48 hours unless contraindicated.
- Patients will receive ketorolac q 6 hours for 48 hours, at the discretion of the surgical team, and if not contraindicated.
- Infusions of dexmedetomidine or ketamine will not be used in either arm
- All patients will receive our intra-operative maintenance fluid management using a balanced salt solution guided by static and functional hemodynamic parameters (stroke volume variation or pulse pressure variation).
- The anesthesia team will determine a range of appropriate mean arterial pressures (MAPs) under anesthesia for each patient based on all available information and maintained with fluids and/or pressors per our usual anesthetic care.
- Blood loss will be replaced with colloid per our usual clinical practice until transfusion criteria are met (HB < 7mg/dl or evidence of hemodynamic instability).

End of Case:

The standard post-operative epidural medication, a combination of bupivacaine 0.05% and fentanyl 5mcg/ml or similar as clinically feasible, will be started at 6 mL/hour following a bolus of 6 mL (for patients on the non interventional GA arm) after fascial closure for all patients. Patients on the intervention arm will have their epidural medication changed over at that time.

Patients will be extubated in the OR if possible or in the Post Anesthesia Care Unit (PACU) and then transferred from the PACU to the floor at the discretion of the surgical service.

Since patients on both arms will have the same epidural medication running at the end of the case (bupivacaine 0.05% and fentanyl 5mcg/ml or similar as clinically feasible), any patient who awakes experiencing pain will have their epidural redosed with a 6ml bolus up to 2 doses. If pain relief does not occur, participants will be treated with intravenous opioids.

All patients will receive the usual standard of care for post-operative epidural management at MSK as described in section 4.2.

Prolonged low blood pressure will be supported with a low dose vasopressor infusion in addition to judicious fluid management, if necessary.

Post-operative pain will be evaluated by a member of the Nursing department first and then by a member of the Anesthesia Pain Service if intervention is necessary, per usual practice, and treated according to the institutional standard of care for patients with epidurals. (See Section 9 Assessing Epidural Function Post Operatively)

Data will be collected as described below and patients will be analyzed secondarily by the final pathology of their tumor for survivorship evaluation. Although pre-operative pathology is

often known, there are occasions where the pre-operative pathology is incorrect or foci of adenocarcinoma are unexpectedly found. Analysis will, therefore, be done on the final pathology.

Patients who are found to have unresectable disease will be removed from the study as they will not undergo the pancreaticoduodenectomy. Patients with a malfuctioning epidural catheter intra-operatively will be analyzed on an intention to treat and as treated manner.

4.2 Intervention

The goal of the study intervention arm is to provide an anesthetic using the epidural intraoperatively which decreases post-operative complications and supports immune function as described above and minimizes the stress response to anesthesia, surgery and pain. We plan to limit narcotic use to up to 2 mcg/kg of fentanyl during induction on the intervention EG arm and provide adequate analgesia with epidural medication as well as intravenous ketorolac and acetaminophen at the surgeons' discretion. The epidural will be continued post-operatively with a standard analgesic regimen for all patients per usual standard of care at MSK (a combination of bupivacaine 0.05% and fentanyl 5mcg/ml or similar as clinically feasible), started at 6 mL/hour following a bolus of 6 mL after fascial closure. This differs from the standard arm which will receive our usual general anesthetic intraoperatively with no restriction on opioid dose and using the epidural catheter for post op analgesia only. Neither group will be given intraoperative infusion of ketamine or dexmedetomidine.

EG Arm: Intraoperative

Patients will have general anesthesia induced in a standard fashion with propofol, rocuronium or vecuronium and up to 2mcg/kg of fentanyl IV. No other intravenous, intra-operative opioids will be given if possible. Acetaminophen and ketorolac will be used at the discretion of the surgical service.

After induction and intubation and before surgical incision, patients randomized to the EG arm will receive from 5 to 10 ml of 0.125% preservative-free (PF) bupivacaine with fentanyl 5mcg/ml through the epidural catheter in divided doses if hemodynamically tolerated.

Anesthesia for the intervention arm will be maintained with sevoflurane in oxygen and air to maintain a BIS reading in the range of 40 – 60 per the company's recommendation. A standard epidural infusion of bupivacaine 0.125% with fentanyl 5mcg/mL will be started at 6 ml/hr. The rate will be adjusted higher or lower, depending on patient hemodynamic response. MAP will be maintained within a range of mean arterial pressures (MAPs) which have been determined to be appropriate by the anesthesia team for each patient based on all available information before randomization, using a combination of intravenous fluids and pressors at the discretion of the anesthesia provider.

After fascial closure, the epidural infusion will be changed to the standard post-operative epidural Patient Controlled Epidural Analgesia (PCEA) (typically a starting basal rate of 6

ml/hr using a combination of bupivacaine 0.05% and fentanyl 5mcg/ml or similar as clinically feasible). The patient will be transferred to the PACU.

In PACU, acetaminophen 1gm q 8 hours and/or ketorolac 15mg IV q 6 hours will be continued for 48 hours at the discretion of the surgical service and if not contraindicated. The epidural will be utilized and assessed and will be discontinued by the anesthesia pain service per pain service protocol. The quality of the analgesia will be evaluated by a member of the Anesthesia Pain Service and/or Nursing on the PCA documentation form.

GA Arm: Intraoperative

Patients randomized to the GA arm will receive our standard anesthetic induction and maintenance using propofol, rocuronium or vecuronium, fentanyl and sevoflurane. There will be no limit to fentanyl dosing on this arm. Their epidurals will be started with the standard pain service epidural analgesia infusion (typically a starting basal rate of 6 ml/hr with a 6 ml bolus using a combination of bupivacaine 0.05% and fentanyl 5mcg/ml or similar as clinically feasible) when the abdominal fascia is closed. The epidural will be continued post-operatively as described above. The quality of the analgesia will be evaluated by a member of the Anesthesia Pain Service and/or Nursing as above. Acetaminophen and ketorolac will be used at the discretion of the surgical service.

Common to both EG and GA Arms:

Pre-operative

For both arms and prior to OR arrival, the anesthesia team will determine a range of mean arterial pressures (MAPs) appropriate by the anesthesia team for each patient based on all available preoperative information. MAP will be maintained within this range with vasopressors and fluids as guided by functional hemodynamic parameters intraoperatively.

Post-operative

The epidural (standard pain service epidural analgesia infusion described above) will be titrated as per the usual institutional pain service practice with a goal of minimizing Numerical Rating Scale for Pain (NRS) levels to a value acceptable to the patient. Upon initial complaint of pain, the bedside RN will encourage the patient to utilize the PCEA. Epidural titration evaluations will be based on daily assessments by a member of the anesthesia pain service. Titration will occur according to institutional practices and may include increasing or decreasing the bupivacaine concentration, increasing or decreasing the opioid concentration, changing opioid, or increasing/decreasing volumes administered, as determined by the pain service provider or nurse practitioner.

Post-operatively the pain service will provide a daily progress note that includes a report of any epidural-related side effects (nausea, vomiting, itching, mental status changes), tolerance of oral intake, proper functioning of the epidural catheter and catheter

complications, including infection, hematoma, and abscess. Nursing will provide the RASS score (for sedation), and respiratory insufficiency (the respiratory rate). Pain Scores at rest and with movement will also be documented by Nursing using a Numeric Pain Rating Scale (NRS) on the Analgesic Infusion Form.

Should pain control remain inadequate, the patient will be converted to an intravenous patient-controlled analgesia (IV PCA) regimen at the discretion of the pain service provider. Failed epidurals (see treatment/intervention plan) will be documented as a post-operative variable.

In PACU, acetaminophen 1gm q 8 hours will be continued for 48 hours with ketorolac 15 mg IV q 6 hours at the discretion of the surgeon for up to 48 hours. The epidural will be utilized per our usual MSK guidelines and can be discontinued with orders from the anesthesia pain service, and the patient switched to oral pain medication.

On the inpatient floors, nurses assess all adult patients for the presence of delirium upon admission to the floor and every subsequent shift until discharge. Individual notes are documented in CIS and there is also (under flow sheets) the *nursing delirium assessment* capturing info for each day and the details of the CAM (Confusion Assessment Method) tool.[93-96]

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

There will be no new therapeutic or diagnostic agents used as part of this study. As all medications are standard and are not experimental, all drugs and materials will be obtained through the standard source of supply at MSKCC. All drugs shall be prepared in the usual fashion, according to routine protocols and guidelines. Epidural catheters will be obtained from The Department of Anesthesiology and Critical Care Medicine using the supplier at the time of the intervention.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Adult patients ≥ 18 years of age who can provide informed consent
- Scheduled for pancreaticoduodenectomy

6.2 Subject Exclusion Criteria

- Pregnancy
- History of documented anaphylaxis or contraindication to any of the study medications
- Significant cognitive impairment or documented psychologic impairment

- Contraindication to epidural per Pain Service guidelines Use of a sustained release opioid medication such as long-acting morphine, fentanyl patches, methadone, and buprenorphine within the last 3 months
- Post randomization exclusion will occur if the patient is found to have unresectable disease at laparotomy and therefore will not have the potential for the same post-operative complications.

7.0 RECRUITMENT PLAN

The eligibility and exclusion criteria do not discriminate either explicitly or implicitly against gender, race or ethnicity.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator or the research team at MSKCC. If the investigator is a member of the treatment team, s/he will screen the patient's medical records for suitable research study participants and discuss the study and their potential for enrollment.

The principal investigators may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

All patients scheduled to undergo pancreaticoduodenectomy who meet eligibility criteria will be approached for participation in the study during the surgical or anesthetic pre-operative visit by a member of the research team. Details pertinent to the trial, the expected outcomes and the associated risks and potential complications will be discussed before enrollment. Informed consent will be obtained by a consenting professional and documented in the patient's chart. Study subjects will not receive any compensation for participation in the study. There will not be any additional costs for the patients derived from participation.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for the screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons we seek a (partial) limited waiver of authorization for the purposes of:

1. Reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process
2. Conversing with patients regarding possible enrollment
3. Handling of PHI contained within those records and provided by the potential subjects
4. Maintaining information in a screening log of patients approached (if applicable)

8.0 PRETREATMENT EVALUATION

All patients will be evaluated by an attending surgeon in the Hepatopancreaticobiliary service. Extent of disease and potential resectability will be determined using a variety of cross-sectional imaging and other studies that will vary depending on the underlying diagnosis. Once a patient is determined to be a candidate for pancreaticoduodenectomy and is otherwise eligible, the patient will be approached regarding participation in the trial. Prior to operation, the following will be performed, all standard before any pancreatic resection:

1. The patient will sign informed consent for the surgery
2. The patient will have a complete history and physical examination
3. Patient demographics will be recorded
4. Pre-operative testing will be obtained per usual MSKCC guidelines
5. Formal medical evaluation for pre-operative clearance will be obtained if warranted
6. Chest radiography or computed tomography scans will be done as per surgeon
7. For women between the ages of 11 and 50, a negative serum pregnancy test within 14 days prior to surgery or a negative urine pregnancy test on the morning of surgery will be obtained

9.0 TREATMENT/INTERVENTION PLAN

The procedures utilized during this trial incorporate routine anesthesia and post-operative surgical practices for patients undergoing proximal pancreatic resection at our institution. None of the interventions are outside the scope of standard peri-operative care.

Epidural Insertion

The patient will be informed of the intended procedure. The procedure and the risks involved will be reviewed with the patient, and all questions will be answered before proceeding. Consent for the procedure will have been obtained as part of consent for participation in the study as well as implied in the consent for surgery.

After evaluation by the pain service and administration of sedation, the epidural catheter will be placed per usual pain service protocol. Epidurals are typically placed in the sitting or lateral position using a loss-of resistance technique to either air or saline. Epidurals will be placed at dermatomes ranging from T6 to L1 as is deemed technically feasible by the Anesthesia Pain Service. During performance of the epidural block, should a “wet tap” or a “bloody tap” occur, another attempt will be made through either a higher or lower intervertebral space. All attempts at epidural insertion will be noted, including those that are unsuccessful. If unable to place the catheter successfully, patients

will be provided with an IV PCA but recorded as a PCEA failure. Those patients who do not have an epidural catheter successfully placed will be withdrawn from the study. Prior to the insertion of epidural catheter at the Pre-Surgical Center, randomization will occur using CRDB on the day before surgery by the Research staff. Patients receiving EG will be dosed at the beginning of the case prior to surgical incision as described in section 4.2. All patients will have a combination of local anesthetic (bupivacaine) and an opioid (fentanyl) using standard concentrations routinely used by Anesthesia Pain Service post-operatively as described in section 4.2

Intra-Operative Considerations

According to our current practice, induction and intubation will be carried out in a standard fashion and as described in Section 4.2 Intervention. The patient will be placed on positive pressure ventilation. An additional intravenous catheter may be placed per usual Anesthetic practice. Patients may have an arterial line placed during surgery as clinically required for hemodynamic monitoring.

All patients will have continuous monitoring of heart rate, blood pressure, electrocardiogram tracing, end-tidal carbon dioxide, oxygen saturation, temperature and BIS or other cerebral monitor. Blood loss and urine output will be recorded. All care will be per usual standard of care at MSK.

The anesthetic technique will be according to treatment arm as described above in Section 4.2. Patients on the EG arm will be evaluated for epidural function intraoperatively by monitoring the patient's need for additional depth of general anesthesia. This information will be documented and the epidural will be evaluated post operatively as described below.

Post-operatively, all patients will be transferred to the PACU and then to the surgical ward at the discretion of the treatment team. Epidural analgesia will be provided as described in Section 4.2.

Assessing Epidural Function Post-operatively

If there is concern for epidural malfunction, defined as inadequate pain control in the PACU despite adequate use of the epidural and after 3 CABs, lidocaine 1% will be administered (5-10ml as tolerated by hemodynamics) and then pain relief will be documented, when achieved. The pain service will assess epidural function post-operatively as per their protocol.

Upon initial complaint of pain, the bedside RN will encourage the patient to utilize the PCEA. The RN may also give additional boluses through the epidural. If the patient still complains of pain, the pain service will be consulted. Lidocaine 1%, 5 – 10 mls can be given by the pain service to assess epidural function. Pain scores will be documented before and after interventions. Ketorolac may be added at the discretion of the surgical service. If patient is still without relief, IV opioid may be utilized to supplement pain management.

Epidural Failure

If epidural placement fails pre-operatively the patient will be withdrawn from the study. If epidural failure is suspected intra-operatively because of increasing requirements for general anesthesia, this will be noted in the intra-operative record and the epidural will be assessed as described above. If it is felt that the epidural is not working adequately post-operatively, the catheter will be removed and the patient will be analyzed on an intention to treat basis.

Epidural Removal

Epidural catheters are assessed daily for function and will be discontinued per usual MSK guidelines. Low molecular weight heparin (LMWH) medications will not be administered to patients enrolled in the trial. Should LMWH heparin have been prescribed, an interval of at least 24 hours must pass prior to removal of the epidural. Other anticoagulants (if prescribed) will be handled per usual protocol of the pain service as described here: http://vsmskpweb02:9068/painservice/guides/anticoags.htm) Routine subcutaneous unfractionated heparin will be used as standard Deep Vein Thrombosis (DVT) prophylaxis and will not be discontinued for catheter removal as per institutional standards. Epidural catheters will be removed per usual pain service protocol, usually on POD 3 or 4, or sooner if not functioning. Documentation and time of removal will be documented by the Anesthesia Pain Service in their routine notes.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

- Pre-operative data will be recorded, including name, medical record number, case number, date of birth, weight, height and laboratory values.
- Pre-operative vital signs will be recorded including MAP.
- Standard intra-operative monitoring as described above will be carried out for all patients.
- Assessment and recording of all complications for the primary endpoint, intra-operative and post-operative; the latter includes any complications occurring on, or after, POD0 (includes intraoperative complications) until POD 90.
- Estimated operative blood loss and urine output will be recorded.
- Cumulative intra-operative and post-operative volume of IV fluids used will be recorded (colloid and crystalloid will be recorded separately).
- Peri-operative blood product transfusion will be recorded.
- Post-operatively the pain service along with nursing will provide a daily progress note that includes a report of any epidural-related side effects (nausea, vomiting, itching, sedation (RASS), respiratory or mental status changes), tolerance of oral intake, proper functioning of the epidural catheter and catheter complications, including infection, hematoma, and abscess.
- Pain Scores will be documented by Nurses using a NRS on the Analgesic Infusion Form.
- A complete blood count will be obtained for three days, or until the day of epidural removal.
- If applicable, daily nasogastric tube (NGT) drainage volume and duration of NGT use will be recorded.
- Day of Foley catheter removal (as per MSKCC protocol) and urinary retention will be recorded.
- The day of tolerance of oral intake of fluids more than 400mL/24hrs will be recorded.
- The day of tolerance of solid food will be recorded.
- The day of passage of flatus and/or feces (return of bowel function) will be recorded.
- Assessment of post operative delirium by nursing using the CAM^{99} tool will be performed once per 12 hour shift and documented in the Nursing Delirium Assessment Flowsheet. (Appendix 2.)
- The day of meeting discharge criteria as well as the actual day of discharge will be documented.

11.0 TOXICITIES/SIDE EFFECTS

The use of an epidural catheter has rarely been associated with severe complications. The incidence of complications, such as nerve damage, epidural hematoma and CNS infection

occurs is less than 1 in 10,000 patients.[100] Suspicion of an epidural hematoma or abscess, according to the institutional practices, necessitates imaging (MRI of the spine) for diagnosis and subsequent evaluation from the neurosurgery service. The differences in anesthetic management are within accepted peri-operative standards and should not pose any additional morbidity to the patients enrolled.

For data collection, all complications of grade 3 or higher, including those felt to be associated with the epidural catheter, as defined by Martin et al[101] and based on Clavien et al[1,2,102] and Dindo,[3] will be collected and reported to the IRB within 5 days as is standard practice. The Hepatopancreaticobiliary (HPB) service runs a biweekly meeting in which all complications are discussed and prospectively recorded into the Memorial Sloan Kettering Surgical Secondary Events Program Database. An anesthesia research study assistant will query the Memorial Sloan Kettering Surgical Secondary Events Program Database at 30 days post-operatively to collect morbidity data for patients enrolled in the study.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary objective of this study is:

To determine whether EG anesthesia, as opposed to GA, affects the incidence of grade 3 or greater complications in patients undergoing pancreaticoduodenectomy and will be assessed during the patients' hospitalization, readmissions, and follow-up reports from outside institutions sent to the surgeon's office. Complications will be graded in severity according to the MSKCC Graded Post Operative Complications Criteria based on the modified Dindo, Clavien classification of surgical complications, a grading system commonly used for this procedure.[3,4] This classification grades complications from 1-5, with Grade 1 complications requiring bedside intervention. Grade 2 requires moderate interventions, such as intravenous medications. Grade 3 requires either a surgical, endoscopic or interventional radiology procedure for treatment. Grade 4 results in chronic deficit or disability. Grade 5 complications result in death. The criteria can be found at on the MSK intranet at https://one.mskcc.org/sites/pub/surgery/Pages/Secondary-Events.aspx. Complication data will be collected for 90 days post operatively.

The secondary objectives are:

1) to determine whether EG anesthesia affects overall survival at 2 years, based on the data showing that the EG technique as outlined has less of a detrimental effect on the patients' immune systems. Patients who have a pathologic diagnosis of pancreatic adenocarcinoma will be evaluated for this endpoint and the survival data and date of death obtained from the CRDB status update report.
2) to evaluate the effect of an EG technique on LOS.

The exploratory objectives is:

To determine if EG decreases the incidence of post operative delirium as compared to GA. This will be assessed by nursing once per shift (twice daily) using the CAM tool and documented in the Nursing Delirium Assessment flowsheet.

13.0 CRITERIA FOR REMOVAL FROM STUDY

A subject may be removed from the study at any time if the attending surgeon or anesthesia provider deems it necessary for patient safety, or if the patient expresses desire to be removed. If a patient is transferred to the Intensive Care Unit (ICU), s/he will have that recorded as a Grade 3 complication for the primary endpoint. Management will continue in the patient's best interests and according to ICU guidelines.

Any patient who experiences any complication intra-operatively related to the epidural will have the medication stopped and will continue with GA. Any patient who experiences any complication post-operatively related to the epidural catheter will have that catheter evaluated by the pain service and removed if necessary and will then continue with IV PCA. Those patients will continue on study and analyzed as intention to treat.

14.0 BIOSTATISTICS

This is a randomized comparison of Epidural-General Anesthesia (EG) versus the standard of care General Anesthesia (GA), both with post-operative epidural analgesia, among patients who undergo Pancreaticoduodenectomy. The primary endpoint is major post-operative complications (Grade 3 or higher). Results from a previous trial indicated a 33% major complication rate in the GA arm (proportion of patients with Grade 3 or higher post-operative complications).[6,7] Hence, we are interested in a decrease in complication rate to 20% in the EG arm.

The evaluable sample size is 366 patients (183 per arm). The randomization will be 1:1 into two arms, stratified by neoadjuvant chemotherapy status (yes/no). The proportion of patients who experience a major complication will be estimated separately for each arm. We will use a Cochran-Mantel-Haenszel test after adjusting for neo adjuvant status to determine the association between treatment arm and the proportion of patients who experience major complications. Although our primary analysis is based on a Cochran-Mantel-Haenszel test, the power calculation is based on an un-stratified Chi-square test, which provides a more conservative estimate of the required sample size. A sample size of 366 provides 80% power for detecting a decrease from 33% to 20% major complication rate with two sided type I error rate of 5% between the two arms. This reduction was selected as the point at which the benefit of EG would warrant a change in peri-operative practice.

This sample size also allows for one interim analysis at halfway through enrollment, using Lan-DeMets spending function with O'Brien-Fleming boundaries for both efficacy and futility. If $p \leq 0.002$ at the interim analysis, then enrollment will stop with the conclusion that the EG significantly reduces major complication rate. If $p \geq 0.0719$ at the interim analysis, enrollment will stop for futility with the conclusion that there is no evidence that EG significantly decrease major complication rates. If $0.002 < p < 0.719$, the trial will continue to completion, and we will conclude that EG significantly reduces

major complication rates if p≤0.049. The boundaries above are based on the planned interim analysis with 50% of the data collected. The actual timing of the interim analysis will correspond to when the DSMB meets; hence, the final stopping boundaries will be calculated based on the information fraction at the time of the actual interim analysis.

Evaluable patients are randomized patients who completed surgery without pre-specified violation of intra-operative criteria, specifically if the patient was found to be unresectable in the surgical room. We anticipate the surgical unresectable rate to be 20%; hence, over-accrual may occur in order to ensure at least 366 evaluable patients for 80% power. The number of patients who are excluded due to unresectability will be summarized by arm and compared using the chi-square test. Based on an expected accrual of ten patients per month, we anticipate the time to completion to be 3 to 4 years. Follow-up will continue for at least two years for each patient (to establish 2 year survival).We will utilize logistic regression to estimate the association between the treatment arms and major post-operative complications, after testing for potential peri-operative/post-operative confounders such as co-morbidities, neoadjuvant chemotherapy status, and adjuvant chemotherapy status.

The secondary endpoints include overall survival at two years and LOS, defined as duration between operation (POD 0) and discharge from the hospital. Overall survival of patients will be summarized by the Kaplan-Meier approach in each arm. Median survival and 2-year overall survival will be presented, along with 95% confidence intervals for the entire cohort and the subset of adenocarcinoma patients. The comparison of interest in terms of overall survival will be performed among patients with adenocarcinoma (estimated to be approximately 60% of population) and based on the final pathology. Overall survival will be compared between the two arms using the log-rank test. Cox proportional hazards models will be utilized to assess the association between treatment arms and the survival endpoint, including potential adjustment factors (co-morbidities, neoadjuvant chemotherapy, and adjuvant chemotherapy).

Analysis of the secondary endpoint of LOS will utilize the two-sample t-test to compare the two arms (with appropriate transformation of the data based on distribution of the endpoint) in the entire cohort. Linear regression will be utilized to assess the relationship between treatment arms and LOS, including potential adjustment factors (co-morbidities, neoadjuvant chemotherapy, and adjuvant chemotherapy).

As exploratory analyses, we will compare the two treatment arms in terms of one additional outcome in the whole cohort: post-operative delirium status (measured daily until POD4). Delirium status will be analyzed with logistic regression including treatment arms and other potential adjustment factors (co-morbidities, neoadjuvant chemotherapy, and adjuvant chemotherapy).

Analyses will be performed under the modified intent to treat (m-ITT) principle: all evaluable patients (as described above) will be analyzed in the randomized arm. Additional results from as-treated analyses (based on actual treatment the patients received) will be reported.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

The study will be conducted in a prospective randomized fashion. During the registration process, registering individuals will complete a protocol specific Eligibility Checklist. After eligibility is established and consent is obtained, patients will be registered as described in Section 15.1.

Randomization will occur on the day before surgery, prior to the placement of epidural catheter at the Pre-Surgical Center. Randomization will be done using randomly sized permuted blocks. There will be a total of 366 patients recruited for this study with 183 patients in each arm. Patients will be approached and consented during a pre-operative clinic appointment. Randomization will be done in a 1:1 fashion to either the EG or GA intra-operative management using CRDB. and stratified to neoadjuvant chemotherapy status (yes/no). The use of the post-operative epidural for analgesia will be common to all patients.

16.0 DATA MANAGEMENT ISSUES

A clinical research coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, patient registration, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization and coordination of the activities of the protocol study team. The CRC will be integrated into current weekly and monthly meetings where complications are recorded, procedures reviewed and outcomes documented. The PI will personally meet with the CRC on a weekly basis to assist with and review the collection and entry of data.

All collected data will only be used for the purposes of the study. It will be maintained in a confidential clinical research database by research study personnel only under the direct supervision of the principal investigator. The database will be kept in a password protected computer and will not be transferred outside the hospital network. A minimum dataset will be kept in CRDB. The data will be linked to the patients by means of unique tracking subject numbers, the key to which will also be password protected and only to be accessed by research personal. Data will be reported to the IRB as required.

DATA TO BE COLLECTED

- Name

- MRN
- Date of birth
- Date of operation
- Sex
- ASA status
- Race
- Height
- Weight
- BMI
- Presence of pre-operative biliary stent
- Comorbidities
- Medications
- Neo adjuvant chemo
- Labs
    - CBC (daily x 3 days)
- Volume and types of fluids intraop, including blood products
- Estimated blood loss
- Urine output and presence of urinary retention
- Use of drain
- NGT drainage, if used
- Pancreatic consistency
- Pancreatic duct size
- Biliary duct size
- Reconstruction and pancreatic anastomosis
- Surgery start and end times
- Pathology including grade
- Stage of disease
- POD NGT is removed, if used
- POD patient tolerates liquids 400ml or greater
- POD patient tolerates solids
- POD Foley catheter is removed
- POD patient passes gas or feces
- Presence of delayed gastric emptying[103]
- Post-operative pain scores twice daily x 3 days
- Function/failure of epidural catheter
- POD epidural catheter is removed
- Grade 3 or greater complications as described according to the MSKCC Graded Post-operative Complications Criteria
- CAM tool delirium assessment twice daily[99]
- Overall 2 year survival for patients with adenoca
- Date of death
- Cause of death (if known)

- POD patient is ready for discharge
- POD of discharge
- LOS
- Administration of adjuvant chemo

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random sample data quality and protocol compliance audits will be conducted by the study team at a minimum of two times per year, more frequently if indicated.

The principal investigator will maintain final responsibility for the maintenance, quality and integrity of all data collection during the study and during the final analysis of data. Breaches of protocol, problems with eligibility, informed consent or discrepancies in data accuracy will be reported to the IRB at MSKCC as required.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the Document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials," which can be found at: http://cancer.gov/clinicaltrials/conducting/dsm-guidelines. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http:/mskweb5.mskcc.org/intranet/assets/tables/content/359709/DSMPlans07.pdf.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g. protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control. In addition, there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g. NIH sponsored, in house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

- The responsible PI will ensure that this study is conducted in agreement with the declaration of Helsinki (Tokyo, Venice, Hong King, Somerset West and Edinburgh amendments). The study will seek to protect the rights of human subjects in every way.
- The potential risks, including adverse drug reactions and potential benefits in terms of post-operative recovery will be discussed in detail with the patients.
- Potential side effects will also be discussed with the patients.
- No patient will be required to participate in the study and participation, or refusal to do so, will not affect the patient's care or treatment.
- The patient will not incur any financial cost as a result of participation in the study.
- Participation will be purely voluntary, and subjects will not be reimbursed for participation in the study.
- Throughout the study, patient confidentiality will be maintained. No results of the study will be presented or discussed in a fashion that will allow identification of a particular patient in the study.

All adverse events will be fully disclosed to the IRB in a timely fashion as required.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/ intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of event. All other SAEs must be submitted within 30 calendar days of event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols:

The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office.

17.2.1

There is no additional SAE reporting information required by the drug supplier.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix 1.

Grade 3 is a standard and validated level of complications defined as “major.” It refers to the degree of intervention required to treat the specific event. Major complications are considered those Grade 3 and above.

MSKCC Graded Post-operative Complications Criteria[2-4,102]

0 No complication.
1 Complications requiring minor intervention: oral antibiotics, bowel rest, basic monitoring, supportive care.
2 Complications requiring moderate intervention: intravenous medications (antibiotics, antiarrhythmics, etc.), TPN, prolonged tube feeding, chest tube insertion.
3 Complications requiring hospital re-admission, surgical intervention, radiologic intervention, ICU admission, intubation/ventilatory support, bronchoscopy, pacemaker placement.
4 Complications resulting in chronic disability, organ resection, enteral diversion.
5 Complications resulting in death.

Appendix 2.

CONFUSION ASSESSMENT METHOD (CAM) SHORTENED VERSION WORKSHEET

EVALUATOR: DATE:

I. ACUTE ONSET AND FLUCTUATING COURSE

a) Is there evidence of an acute change in mental status from the patient's baseline? No ____ Yes ____

b) Did the (abnormal) behavior fluctuate during the day, that is tend to come and go or increase and decrease in severity? No ____ Yes ____

II. INATTENTION

Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said? No ____ Yes ____

BOX 1

III. DISORGANIZED THINKING

Was the patient 's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject? No ____ Yes ____

IV. ALTERED LEVEL OF CONSCIOUSNESS

Overall, how would you rate the patient's level of consciousness?

-- Alert (normal)

-- Vigilant (hyperalert)
-- Lethargic (drowsy, easily aroused)
-- Stupor (difficult to arouse)
-- Coma (unarousable)

Do any checks appear in this box? No ____ Yes ____

BOX 2

If all items in Box 1 are checked and at least one item in Box 2 is checked a diagnosis of delirium is suggested.

Adapted from Inouye SK et al, Clarifying Confusion: The Confusion Assessment Method. A New Method for Detection of Delirium. Ann Intern Med. 1990; 113:941-8. Copyright © 2003 Hospital Elder Life Program, LLC.