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Chapter 8

The Improvement of Care in Patients with Pancreatic Cancer

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Abstract

Introduction: Pancreas adenocarcinoma (PDAC) remains a lethal malignancy with a high-mortality rate and poor long-term survival. The management of PDAC has evolved over the years to incorporate multidisciplinary care and numerous treatment modalities.

Body: We discuss the current standard of care for the management and treatment of PDAC. We also discuss the value of managing PDAC patients with multidisciplinary care, at high volume pancreas centers, with multimodality therapy, and with innovative surgical techniques.

Conclusion: PDAC is an aggressive malignancy. Nuances in the management of the disease can help to improve outcomes.

Keywords: pancreas adenocarcinoma, pancreas cancer, borderline resectable, neoadjuvant therapy, whipple, distal pancreatectomy, robotic surgery

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is currently the 10th most commonly diagnosed cancer in the United States and the third leading cause of cancer-related mortality. It is expected to become the second leading cause of cancer-related death by 2030 [1, 2]. While most of the other more common (lung, breast/prostate, and colon) causes of cancer-related mortalities have shown signs of down-trending throughout the years, PDAC has shown an unfortunate upward trend [3]. The increasing incidence and mortality is likely multifactorial, with increasing environmental exposures, increase in survival age, or any other of the many stratifying risk

factors. Regardless of the factors influencing the increasing risk of acquiring PDAC, the aggressiveness of the disease itself should be a continued target in the attempt to control or decrease the disease morbidity and mortality [3–5]. PDAC has an aggressive tumor biology with a propensity for early metastasis. Less than 20% of patients with PDAC will present with disease amenable to surgical and potentially curative therapy [1, 3].

The reason for the poor survival in PDAC patients is multifactorial. Tumor biology, lack of screening and early diagnostic test, historically morbid surgical interventions, and systemic therapies with limited efficacy are factors that have been shown to significantly affect the outcomes of patients with PDAC. The combination of the aforementioned factors has led to pessimism within the medical community about the efficacy of pancreatic disease management [6]. However, several advances have been made over the years; and with such a highly lethal disease, any margin of progress can be a large gain. Some of these advances are related to the improvement in coordination of care to overcome systemic barriers that limit the overall efficacy in caring for the disease; other advances have been technical in nature; and finally, several advances have been made in the approach of systemic therapies.

2. Multidisciplinary management team

One of the primary challenges of the modern healthcare system is the fractured nature in which care is provided [7]. Patients with PDAC may be seen by a primary care doctor or gastroenterologist but may never be seen by a medical or surgical oncologist, depending on disease recognition and provider referral. In order to accomplish a more desirable outcome, a balance must be reached between access to care and the quality of care provided. In a disease presenting with many obstacles, providers having experience in managing PDAC and patients having access to the most advanced therapies, including clinical trials, can make a significant difference in outcomes. Research into these systemic healthcare factors has spurred the production of various causal effect models; one model, in particular, demonstrates the effect of the type of provider in charge of disease management and its impact on the patient receiving expected treatment [7, 8].

Historically, the pessimistic outlook for patients with PDAC has generated skepticism regarding the efficacy of therapy and resection. These attitudes adversely affect proven beneficial disease management involving the utilization of surgical and medical interventions, particularly evident in cases of early stage pancreatic cancer [7, 9, 10]. Bilimoria et al. were able to demonstrate that despite modern improvements in survival after pancreatectomy, 51.7% of Stage I patients did not undergo surgery for potentially resectable pancreatic cancer even after accounting for patients who did not undergo surgery due to severe comorbidities, advanced age, or patient refusal. Patients were less likely to undergo surgery if they were older, were black, had lower annual incomes, had less education, or were on Medicare or Medicaid [6]. This difference in management exhibits a significant correlation with the racial and socioeconomic discrepancy. Similar discrepancies in care due to race and socioeconomic status have been reported by several studies [11, 12]. Patients were more likely to receive surgery at

academic institutions, high-volume hospitals, and National Comprehensive Cancer Network or National Cancer Institute (NCCN/NCI) centers. This was the first study to describe and characterize such striking underuse of pancreatectomy while identifying factors predicting underutilization [6, 7, 11].

While the initial referral is critically important, once a patient has been referred to a surgeon or an oncologist, the provider's level of experience in managing PDAC is of equal, if not more, significance. The early involvement of a pancreatic cancer specialist has been proven to exhibit a most marked effect on early-staged disease patients [7–9]. Physicians who care for PDAC patients on a regular basis have several advantages over those who rarely treat the disease. These advantages are evident when comparing perioperative and intraoperative statistics, such as estimated blood loss, case duration, length of postoperative hospital stay, perioperative death, and need for reoperations [13]. Evidence shows us that increased surgical or disease management experience decreases disease morbidity [7, 13]. Improving morbidity, in an already highly morbid disease, will help alter the pessimism surrounding PDAC through recognition of some impactful management options.

It is known that surgery is the only curative therapy for PDAC [6]. It is also known that either adjuvant or neoadjuvant therapy is the patient's best shot for a prolonged survival [7, 14, 15]. Recent evidence regarding oncological diseases has shown that the multidisciplinary approach will have beneficial effects on disease management [7–10]. As such, the development of multidisciplinary treatment teams and multimodal therapeutic interventions has become the benchmarks of PDAC patient management. Most patients, regardless of stage, require multiple subspecialty services including surgery, gastroenterology, medical and radiation oncology, nutrition, and palliative care [7]. These teams allow for the development and collaboration of specialty expertise, bringing a variety of perspectives to each PDAC case.

Although specific team composition may vary throughout center sites, studies continue to illustrate the overall correlation of this model with improved quality of care. Studies assessing the efficacy of this model have demonstrated decreased diagnosis-to-treatment time, increased probability of receiving treatment, prolonged survival, increased involvement of multimodality therapy, and increased enrollment and participation in clinical trials. One significantly impactful factor in this model is the decreased diagnosis-to-treatment time. Evidence shows that approximately 80% of early Stage I/II diagnosed PDAC patients, not seen in specialized, multidisciplinary centers, fail to receive a potentially curative surgery or life-prolonging treatment [8, 9]. Of early-stage (Stage I/II) disease patients who did not receive surgical resection, only 28% had a surgical referral. Of early-stage patients who had received surgical intervention, it was noted that referral to a pancreatic disease specialized center or surgeon significantly impacted whether surgery was performed; 80% of early-stage patients seen in a specialized pancreatic disease clinic received surgery, whereas only 20% of comparable patients *not* seen in a specialized clinic received surgery [7, 16].

Another factor to consider multidisciplinary approach to caring for pancreatic cancer patients is the greater accessibility and probability of the use of multimodal therapy. While studies continue to show variance in the statistical significance of multimodal therapies, they remain an important element in the development of more effective interventional therapies for such

an aggressive cancer. Correspondingly, the inclusion of patients in clinical trials is another benefit of multidisciplinary team centers. Studies have shown up to a two times higher likelihood of patients participating in a clinical trial when seeing a multidisciplinary team. This plays an important role in acquiring a greater understanding of the disease and the development of more effective therapies [7, 16].

Ultimately, the historical lack of multidisciplinary care is only one of multiple factors attributed to the poor survivability curve seen in PDAC patients. However, in recent years, changes in the management of PDAC have started to shift the curve toward showing improvement in the acute care of patients as well as increasing the number of long-term outcomes [17].

3. Defining the disease

The diagnosis of PDAC often remains a challenge. The utilization of various imaging modalities in the diagnosis and staging of PDAC continue to be utilized. Computed tomography (CT), ultrasonography (US), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS) are the routinely used modalities that are relatively accessible in hospitals and specialized cancer centers. As the management of PDAC has advanced and become more aggressive analogous to the nature of the disease, imaging modalities play an important role, not only as a noninvasive option in the diagnostic phase of the disease but also in the determination of disease burden, resectability, and the monitoring of treatment efficacy [18].

CT scanning is the accepted first line investigative modality in PDAC suspected patients. This modality is usually preferred because it provides high-resolution/quality images and relatively wide availability, and its complete studies are relatively quicker than other high-resolution counterparts. CT scans are reported to provide 100% sensitivity and 72% specificity in predicting the resectability of PDAC [19]. This modality also allows for the ability to use a specific image-attaining protocol for more thorough evaluation of the pancreas. This pancreas protocol utilizes thin-sectioned slices and captures images during certain postcontrast injection time frames. Because PDAC is a hypovascular tumor, it is best detected in the late arterial phase at 35–40 s postcontrast injection, when the normal pancreatic parenchymal tissue is most optimally enhanced while the hypovascular tumor is not. At 70-s postcontrast injection, the portal venous system is optimally enhanced, which can prove helpful in assessing any extent of venous involvement and identifying possible liver metastases. These two phases are typically obtained during a pancreatic protocol CT. Of note, when there is a concern for pancreatic islet cell (endocrine) tumor exists, an earlier (20–25-s postcontrast injection), arterial phase scan is usually most beneficial, since these tumors are often hypervascular. Some of these endocrine tumors can be visualized in the portal venous phase as well, and thus dual phases of arterial and portal venous scanning are usually done for suspected pancreatic endocrine tumors. The pancreatic protocol CT scan produces images with PDAC classically appearing as a hypodense lesion relative to the pancreatic parenchyma [19, 20]. On an approximate, 10% of cases where PDAC lesions are isodense on imaging, distinguishing the tumor can be more difficult. Other signs can be present on CT imaging that increase detection of a pancreatic mass.

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Lesions present in the pancreatic head can produce a secondary finding of "double duct" sign, which is the presence of simultaneous dilation of the common bile and main pancreatic ducts. This is due to the tumor in the head portion of the pancreas compressing the ducts causing obstruction and fluid build-up that result in dilation of both ducts. Tumor in the body or tail of the pancreas can result in stenosis and obstruction of the main pancreatic duct, resulting in an upstream dilation of the main pancreatic duct. These signs can be beneficial in distinguishing a more isodense lesion or in the confirmation of a smaller, hypodense PDAC lesion. However, this modality can be limited in its ability to differentiate an isodense lesion and to show possible metastatic disease when denoted by small lesions in certain areas such as the peritoneum or liver [18, 20, 21].

One of the most sensitive and high-quality image producing modalities to date is the MRI. The MRI modality in comparison to CT scans provides greater soft tissue quality. This allows for superiority in imaging of smaller tumors and fatty infiltration of the pancreatic parenchyma, and in distinguishing lesions that would show as isodense lesion on CT scan. The most effective MRI-weighted imaging sequence for assessing the pancreas is the T1-weighted, fat suppressed sequence. In this sequence, PDAC usually appears hypointense [18]. Other sequences (T2-weighted, DWI, and GRE) have been shown to be relatively inconsistent in the PDAC intensity seen on imaging; however, they are still useful in assisting thorough evaluation of the pancreatic tissue. Another advantage of the MRI is the ability to perform a more in-depth examination of the pancreatic ducts utilizing magnetic resonance cholangiopancreatography (MRCP). This technique allows for inspection of the ductal systems and ability to discern small ductal narrowing secondary to a small lesion or to detect confounding etiologies to ductal dilation such as a stone obstructing either the common bile or main pancreatic duct. MRCP, in conjunction with the MRI, can result in more efficacious detection in early stage pancreatic disease by allowing more detailed study of the pancreatic parenchyma and ductal system. Limitations of this modality in the diagnosis and interventional benefits in PDAC disease include significant time for study completion, fairly high cost, easy susceptibility to artifact and difficult accessibility in areas with limited resources [18, 21].

Ultrasonography (US) is a most likely and readily available modality than all other applicable modalities in visualizing the pancreas. US can also be done very quickly with low cost and increased portability. However, US scan of the pancreas is fairly low in quality, requires specific preimaging preparation for the patient, and requires trained and experienced people for the operation to be most effectively utilized. A minimum 6-h fast is required to better visualize the pancreas; this fast preparation improves visualization by limiting bowel gas and ensuring an empty stomach. The scan protocol evaluates different sectional cuts (transverse, oblique, and sagittal) along the pancreatic duct in the search for signs of obstruction or stenosis. This can often visualize the pathognomonic observation of double duct sign in PDAC of the pancreatic head. The PDAC lesion is often evident as a hypoechoic lesion on imaging. However, diagnostic utility of US is highly dependent upon the operator's training and experience, the burden or progression of disease, and the habitus of a patient [18, 21].

Endoscopic ultrasound (EUS) has been considered as a modality producing highly accurate detection of small (greater than 3 cm) lesions. This modality provides visualization of the

pancreatic tissue and parenchyma from the stomach or duodenum. It allows for higher quality images to be obtained in comparison to standard US. EUS also has the benefit of being able to obtain specimens via fine needle aspiration. On its own, EUS is not highly effective in differentiating a chronic pancreatic disease such as chronic pancreatitis and pancreatic cancer, with evidence showing the accuracy at 76% for detecting cancer and 46% for detecting a local inflammation, whereas the combination of EUS and fine needle aspiration has shown to increase the detection percentage of pancreatic cancer to 90% and above [18]. Limitations of this modality include the necessity of conjoined procedures, including a more invasive, albeit minimally, technique. Fine need aspiration is also not a widely and readily available resource amongst all hospital and care centers.

One of the most important components of a multidisciplinary team is that the presenting state of the disease is agreed upon, and a treatment plan is constructed in accordance with national guidelines for care while also taking into account distinctive patient factors. The expertise of the multidisciplinary team and standardized national definitions regarding disease staging are associating factors best utilized concurrently in determining disease burden and the initial steps in optimizing patient management. Although pathologic staging criteria for PDAC have long been established through the American Joint Commission on Cancer (AJCC), clinical staging criteria has not been as well defined. For an extensive period of time, common language was lacking for defining the degree of tumor involvement with surrounding vasculature and the subsequent classification of whether or not it is safely resectable. From a surgical perspective, the determination for surgical intervention is based on the tumor's determined resectability. By classifying patient tumors as resectable, borderline resectable, locally advanced, and metastatic, the care team is better able to standardize treatment regimens for patients. Furthermore, more defined classifications allow for greater adherence to national guidelines [20, 22].

Although several definitions of resectability have emerged over the years, the most widely accepted classification, which has also subsequently been incorporated in the National Comprehensive Cancer Network (NCCN) criteria, was defined by Callery et al. [22]. They constructed a consensus criterion based on radiographic CT findings in the preoperative staging phase. Resectable tumors are those that (1) had demonstrated no distant metastases; (2) had shown no radiographic evidence of superior mesenteric vein (SMV) and portal vein abutment, distortion, tumor thrombus, or venous encasement; and (3) had shown clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery. Borderline resectable tumors are defined as those that (1) had shown no distant metastases; (2) demonstrated either some venous involvement of SMV/portal vein (a) with tumor abutment with or without (i) impingement and narrowing of the lumen, (ii) encasement of the SMV/portal vein without encasement of the nearby arteries, or (iii) short segment venous occlusion resulting from either tumor thrombus or encasement, (b) but with suitable vessel proximal and distal to the area of vessel involvement, which allows for safe resection and reconstruction; (3) demonstrated some gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis; and (4) demonstrated tumor abutment of the SMA not to exceed more than 180° of

the circumference of the vessel wall. Locally advanced tumors were defined as those that fell outside the definition of borderline resectable. Metastatic tumors were defined as those with any evidence of metastatic disease [22].

Despite the relatively high accuracy in predicting unresectable disease, current imaging modalities still lack indisputable certainty in predicting the degree of resectable disease. A complimentary tool for increasing sensitivity in assessing a tumor's resectability and stage is diagnostic laparoscopy. Per guidelines, for apparent resectable disease, utilization of laparoscopy should be used with clinical predictors that optimize yield including pancreatic head tumors greater than 3 cm, tumors of the pancreas body and tail, ambiguous findings on CT scan, or high CA 19-9 levels (>100 U/mL). In addition, locally advanced and unresectable pancreatic cancer, without radiographic evidence of distant metastasis, should also be further evaluated with laparoscopy in order to rule out subclinical metastatic disease so that the care team's therapeutic management can be optimized [20, 22].

4. High-volume centers

The outside referral to pancreatic cancer specialist, hospital, and institutional volume of patients treated for pancreas cancer matters as well. The volume of patients treated and cases seen directly correlate with the experience gained by the providers in the management care team [13, 23]. The pancreaticoduodenectomy (PD) was classically a very morbid operation with mortality after PD nearing 25% in the 1960s [6, 17]. The morbidity associated with the operation was multifactorial. However, the factor most attributable to the morbidity is the risk of pancreatic fistula development. Often unrecognized, and thus untreated, a pancreatic fistula is the development of an abnormal communication between the pancreas and other organs secondary to the leakage of pancreatic secretions from damaged pancreatic ducts. This communication can prove highly detrimental to the involved organs. A pancreatic fistula substantially contributes to the most morbid complications seen with the operation such as erosion of retroperitoneal vessels and hemorrhage, intra-abdominal abscess, sepsis, multisystem organ failure, and death [24]. Over the years, PD morbidity and mortality have improved significantly, with mortality dropping to less than 3% in some high-volume centers. The involvement of high-volume pancreatic surgical centers has greatly contributed to this decline. Multiple studies have demonstrated a relationship between hospital surgical volume and outcomes for pancreatectomy [24, 25]. Specifically illustrating that as hospital volume for pancreatic surgery increases, perioperative mortality, postoperative complications, length of stay, and overall cost decreases, and long-term survival improves [6]. In 2011, a 10-year observational study (1999–2008) examined the relationship between cancer center volume and particular cancer operations. PD was compared to several other cancer and high-risk operations including esophagectomy, lung resection, cystectomy, AAA repair, and carotid endarterectomy, among others. The study found an increase in the median number of cancer and high-risk operations performed at hospitals. Pancreatic cancer surgery exhibited the greatest observed median increase, with an approximate 200% national increase in the median number of patients receiving pancreatic cancer surgery at each hospital, an increase of 5 patients per

center to 16 per center. This figure is most notably influenced by the 56% national increase in patients seen for pancreatic disease, and the 25% national decrease in the number of hospitals performing the PD procedure, which does not detract from the fact that more pancreatic cancer patients are being seen and more PD procedures are being done. The most encouraging finding is that with this increase in PDAC patients seen and PD cases performed, there has been an almost 20% decrease in the postpancreatectomy mortality (death prior to hospital discharge or within 30 days after surgery). These findings denote a strong correlation observed between the operative risk incurred and the hospital's relevant surgical case volume [25–27]. While some high-risk operations examined in the study showed minimal volume-outcome relationship, there was substantial evidence that the volume-outcome relationship for PD is particularly strong. It has also been suggested that differences in surgical technique, such as margin involvement with resection, might be influential on the volume-based differences seen in PD mortality and morbidity. Resected margins showing cancerous involvement (margin-positive) are a poor prognostic factor after PD. The study found that patients undergoing PD at low-volume pancreatic cancer centers are more likely to have margin-positive resections, either macroscopic (R2), microscopic (R1), or both [26, 27]. These findings support the concept of improved morbidity and mortality of PD at high-volume centers and emphasize the importance of PDAC patient referral to specialized, high-volume centers.

5. Improvement in surgical care of the patient

Over the last 20 years, significant advances in preoperative evaluation, surgical techniques, and postoperative care have reduced the perioperative morbidity and mortality associated with pancreatic surgery. Mortality after pancreaticoduodenectomy has dropped from 25% in the 1960s to less than 3% in some high-volume centers, with recent studies suggesting postresection long-term survival rates approaching 30%.While numerous studies and guidelines establish pancreatectomy as the primary intervention for localized PDAC, pessimism concerning pancreatic cancer disease is the likely cause of continued skepticism in the efficacy of resection. In opposition to this belief, surgeon cumulative and yearly volume in the treatment of pancreatic diseases has emerged as a surrogate marker for quality outcomes. Surgical volume produces surgical experience, and, as Birk et al. illustrated, higher volume pancreatic centers result in lower operative mortality [25]. While the number of pancreatic cancer centers is declining, the increase in case number correlating with the decrease in morbidity and mortality suggests that the market concentration of cases is providing the opportunity to obtain more experience for the surgeons performing them [25]. There has been documentation illustrating that personal surgical volume can affect patient outcome [23, 24]. This concept illustrates the importance of surgical proficiency as a contributing factor on operative morbidity and mortality, despite the complexity or high-risk nature of the operation. High-volume centers offer the opportunity for pancreatic specialized surgeons to become more experienced with the cancer operations as well as more accustomed to varying surgical expectations and complications, thus resulting in reduced operative mortality and improved outcomes. Evidence has emphasized the correlation of operative experience and case load,

surgical benchmarks and the pancreatic surgical learning curve [23–25]. One study looking at approximately 2200 pancreatic surgeries performed during 1984–1991 showed a significant correlation between a surgeon's number of cases done and the mortality rate. Low-volume surgeons (<10 resections) exhibited a 16% mortality rate in comparison to higher volume surgeons (>40 resections), who exhibited a 5% mortality rate (Fisher, list paper). Fisher et al. also showed this concept to be true. The author looked at the first 11-year period of a particular surgeon's pancreatic practice, examining 162 Whipple procedures performed, divided into two categories of low-volume era (0–11 cases/year) and high-volume era (>22 cases/year). Patients in the low-volume era had a higher likelihood of exhibiting one or more complications when compared to patients in the high-volume era (58% low volume vs 46% high volume) (Fisher). Training environment, in addition to case volume, is important in acquiring and strengthening the proficiency desired for preferred pancreatic surgical outcomes [16, 23, 25]. Surgeons at academic or more specialized centers appeared to significantly progress at a greater rate, likely due to the substantial experience of the providers available to initially assist in training or mentoring more inexperienced surgeons.

6. Improvements in perioperative care

The perioperative phases of the surgically treated pancreatic cancer patient have substantially improved due to the establishment of multidisciplinary care teams, the advancement of diagnostic and interventional techniques, and the continued progression of surgical experience and proficiency. While much of this can be attributed to the development of extensive technical modalities and abilities, proper and successful recovery is also an essential factor in improving postsurgical patient outcomes. The enhanced recovery after surgery (ERAS) program is a multimodal strategy that attempts to mitigate functional loss and morbidity, while improving recovery and progression of functional capabilities in the perioperative setting. The pathways included in the ERAS strategy include various preoperative and postoperative recommendations that have significant effect on a patient's morbidity development and hospital course [28].

Significant preoperative strategies include preoperative counseling, preoperative smoking and alcohol cessation, decision to use oral bowel preparation, and anticoagulation and antimicrobial prophylaxis [28–32]. Preoperative counseling, including procedural expectations and postoperative objectives, allows for the subduing of surgical anxiety and fear. This in turn results in improved postsurgical course [28]. Preoperative smoking and alcohol cessation can substantially improve a patient's outcome. At least 1 month of abstainence from smoking and alcohol reduces the otherwise two- to threefold postoperative morbidity increase seen in these patients. Also, this concept results in a considerable reduction in the pulmonary and wound complications often present in this group [28, 29]. Oral bowel preparation is thought to reduce complications of the surgery. However, evidence has shown that there is no clinical benefit to performing mechanical bowel preparation. Data actually show that there is more of an increased risk of dehydration or electrolyte imbalance, particularly in elderly patients [28]. Thus, it is strongly recommended that mechanical bowel preparation not be used as a preoperative strategy. The malignancy of pancreatic disease in conjunction with the major surgical

procedure of PD puts the patient at a substantially higher risk of acquiring a venous thromboembolic event (VTE). The evidence strongly supports the beneficial use of a heparin, preferably low-molecular-weight heparin due to its 1× daily administration, in preventing or significantly reducing the risk of VTE. Standard prophylaxis involves administration 2–12 h prior to surgery and continuation until patient has fully mobilized, with some evidence suggesting benefit of continuation until 4 weeks after discharge. Mechanical preventative measures should also be utilized in even higher risk patients. Preoperative antibiotics are another highly recommended strategy for improving postoperative course and outcome of patients. Usual antibiotic prophylaxis recommended for pancreatic surgery include either 2 g (30 mg/kg peds) of Ancef (cefazolin, first-line), clindamycin(900 mg, 10 mg/kg peds)/vancomycin (15 mg/kg adult/ped) plus gentamicin (5 mg/kg, 2.5 mg/kg peds), or the addition of 400 mg (6 mg/kg peds) Diflucan (fluconazole) for patients at high risk of acquiring fungal infection such as in cases where there is enteric drainage of the pancreas [30]. Evidence indicates that antibiotic prophylaxis should be initiated 30–60 min prior to skin incision for optimal efficacy with repeated doses intraoperatively, depending on half-life of the utilized drug.

It is noteworthy that postoperative strategies are somewhat more extensive; however, strongly recommended strategies include adequate pain control, glycemic control, early diet advancement, early mobilization, and early removal of anastomotic drains (after 72 h). Pain control in the postoperative period is often highly important in patient cooperation with postoperative, recovery goals. While specific evidence for superiority between epidural, patient controlled analgesia, and other intravenous medications is less, proper pain control evidently results in earlier progression through postoperative objectives such as early mobilization. Postoperative morbidity and mortality are greatly influenced and increased by hyperglycemia and insulin resistance. Intensive care unit postoperative patients have been documented to exhibit a lower complication risk with a reduced hyperglycemic rate. Because abdominal surgery is associated with increased levels of insulin resistance, a significant increase in baseline postoperative morbidity risk occurs since the risk of hyperglycemia increases. Insulin administration is important in keeping glucose under control; however, caution must be taken for the prevention of hypoglycemia. While evidence indicating best glucose levels is controversial, basic hyperglycemic prevention will is needed to improve outcomes despite the baseline level [28, 31]. Furthermore, optimizing nutrition, with early diet advancement, in the postoperative period remains a strongly recommended strategy as well. The majority of patients will be able to tolerate oral intake shortly after elective PD. Evidence has shown that early oral intake is safe. Recent evidence has shown that early initiation of regular diet is reasonable and safe, and that enteral tube feeds illustrate no additional or greater benefit. There is also no evidence of improved benefit or safety of provider-controlled diet advancement (e.g., sips of liquids compared to regular diet), and a patient-controlled advancement as tolerated [28]. Another often recommended postoperative strategy is early and/or scheduled patient ambulation or mobilization. Patients should begin mobilizing or trying to ambulate in the morning of postoperative day 1. This strategy significantly reduces standard postoperative complications resulting from patient inactivity such as atelectasis and VTE risk. This can be encouraged through removal of barriers to ambulating or mobilizing such as a foley, and setting incremental patient activity goals on a daily basis, such as laps around the hospital floor, moving

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to a chair for a set period of time, among others. This has shown to reduce the rate of postoperative complications as well as reduce hospital length of stay and improve recovery time [28, 32].

While the aforementioned concepts and strategies prove significant for the management of acute surgical patients, the overall management strategy for a pancreatic cancer patient has substantially changed. Historically, nasogastric decompression postpancreatectomy, particularly PD, was deemed necessary, not only to avoid tension on the gastrojejunostomy but also due to the concern of delayed gastric emptying, which was the most common complication after the procedure. However, it has been shown that foregoing nasogastric decompression after pancreatectomy (both PD and DP) is safe and does not result in increased frequency or severity of postoperative complications, including placement or replacement of a nasogastric tube after surgery. It also has no effect on length of stay or advancement to regular or postgastrectomy diet [33].This evidence aligns with ERAS program recommendations for pancreatectomy patients. Nasogastric decompression should thus be reserved exclusively for selected patients, particularly approximately 10–25% [34] of patients who develop delayed gastric emptying (DGE) after PD.

Another topic of broad and current interest has been the use of intraperitoneal drains after pancreatectomy. Multiple high-volume single-institution studies have shown either no difference or a decreased overall complication rate with elimination of routine drainage. This is likely the result of the elimination of a portal of entry for bacteria and a potential source of strain on the anastomosis, the latter particularly with the use of closed suction drains. However, when routine elimination of drains was evaluated in a multicenter randomized controlled trial, there was an increase in the number of patients that had at least one? Grade 2 complication (drain 52% vs no drain 68%; $p = 0.047$) and a higher complication severity ($p = 0.027$). Not only was there an increase in morbidity, but also there was a fourfold increase in mortality from 3 to 12% in patients undergoing PD without intraperitoneal drain placement. It is important to emphasize that these results apply only to PD patients, but based on the evidence, abandonment of routine intraperitoneal drainage in this group of patients is not safe. More studies are needed to address the safety of early removal of drains in PD in compliance with ERAS protocols. As for DP, the safety of routine elimination of drains is currently being evaluated in a multicenter randomized controlled trial (NCT01441492, clinicaltrials.gov).

Finally, there is a strong recommendation for early removal of perianastomotic drains, usually within 72 h. The anastomotic drains are believed to reduce the consequential effects seen with minor pancreatic leaks. Evidence showed that early removal of a drain in low-risk pancreatic fistula patients (drain fluid amylase <5000 U/L) was associated with a significantly reduced rate of pancreatic fistula formation, abdominal complications and pulmonary complications. There has also been increased scrutiny surrounding whether drain placement is even necessary to begin with. While there is data supporting this strategy, there is also data showing otherwise [32]. Van Buren et al. studied this concept by looking at 137 PD patients in a randomized prospective multicenter trial, 68 with drain placement and 69 without. From the Level 1 data provided, it was shown that elimination of the intraperitoneal drain in PD cases resulted in a significant increase in severity and frequency of postoperative complications. Furthermore,

the study also illustrated a fourfold increase in mortality (3–12%) [35]. This raises skepticism toward findings in the previous literature and supports advocating caution against eliminating the use of drains altogether. However, per ERAS recommendations, early removal of the drain is associated with fewer and reduced rate of complications [28, 35].

These strategies provide a unified protocol for perioperative management of the PD procedure that could likely prove beneficial to centers through reducing postoperative complication rates, time of recovery and hospital length of stay [28, 32]. Ultimately, it is the summation of these factors that contribute to the improvement in the postoperative outcomes of pancreatic cancer patients. While the aforementioned concepts and strategies prove significant for the management of the acute surgical patient, the overall management strategy for a pancreatic cancer patient has substantially changed [23, 25, 28, 32].

7. Technical advances

Many of the advances that are discussed above are system-based and involve the perioperative period of patient care. These have had a tremendous impact on patient outcomes in the treatment of PDAC. But of all the modalities involved, surgery remains the only treatment with the potential for cure in patients with localized pancreatic cancer. Significant improvements in preoperative evaluation and postoperative care have reduced the perioperative morbidity and mortality associated with pancreatectomy. As previously discussed, mortality after PD has dropped significantly and there have also been improvements in long-term survival rates. In addition to these changes, surgical technique itself is progressing and evolving.

In an evidence-based systematic review, Wright and Zureikat identified four key elements that have allowed minimally invasive pancreatic surgery to gain momentum: safety, oncologic efficacy, cost, and reproducibility. Even though the evidence available is not the result of randomized controlled trials but instead on case series matched with cohorts undergoing open procedures, morbidity and mortality have been shown to be comparable between minimally invasive (MI) and open techniques. This applies for both PD and DP and encompasses all modalities of MI techniques: laparoscopy, robotic-assisted surgery, and their institutional variations.

The main concern with the adoption of MI techniques for the treatment of PDAC is undoubtedly oncologic efficacy. A study by Kendrick et al. favored MI technique by demonstrating fewer delays to initiation of adjuvant chemotherapy after laparoscopic PD with similar oncologic survival when compared to that in open procedure. Another study using the National Cancer Data Base demonstrated no difference in oncologic outcomes between laparoscopic and open PD [36]. In the setting of DP cases, Lee and colleagues (reference below) showed similar oncologic outcomes and high rates of R0 resection between open and laparoscopic DP. The mean number of lymph nodes evaluated in the aforementioned series was higher with open DP (15.4) when compared with the minimally invasive techniques (10.4 with laparoscopy and 12 with robotic approach). However, there was no statistically significant

difference in the number of positive lymph nodes evaluated. Although the retrospective design of these studies introduces the possibility of selection bias in terms of patient selection, surgeon preference/experience, and preoperative patient and oncologic characteristics, the available evidence so far demonstrates that laparoscopic and robotic approaches to pancreatectomy do not adversely affect oncologic outcomes and add benefits such as decreased EBL and LOS [37–39]. However, it is important to note that the sources of most of the available literature are high-volume centers, which introduces a potential source of bias and reinforces the importance of patient evaluation and treatment at high-volume centers with multidisciplinary teams.

Cost is one of the limitations of MI pancreatectomy, particularly the robotic technique. However, some authors have shown the robotic technique to be cost effective when the reduction in length of stay is taken into consideration [40, 41]. Additionally, the robotic technical skills are potentially easier to acquire when compared to laparoscopic technique. This is secondary to the advantages provided by stereotactic vision, robotic simulators, and training consoles. The learning curve defined as 80 cases for a reduction in operative time may shorten with time since the operative steps and training techniques have recently become better defined [42].

Another noteworthy technical advancement is the incorporation of vascular resection (VR) with PD. Tseng et al. described five types of venous resection and reconstruction involving the superior mesenteric vein (SMV), portal vein (PV), or superior mesenteric-portal venous (SMPV) confluence. These are tangential resection with saphenous vein patch (V1), segmental resection with splenic vein ligation and primary anastomosis (V2) or with interposition graft (V3), segmental resection without splenic vein ligation and primary anastomosis (V4) or with interposition graft (V5). In their single institution series, Tseng and colleagues demonstrated that properly selected patients with PDAC of the head of the pancreas undergoing VR had a median survival of approximately two years. There was no statistical difference between survival of patients undergoing standard PD and those undergoing PD and VR ($p = 0.177$) [43].

Adequate patient selection for PD with VR has been possible by technological advances in computer tomography and by a multidisciplinary approach involving surgeons and radiologists. While several single center studies [44–46] have demonstrated PD with VR to be safe, a retrospective cohort analysis of the National Surgical Quality Improvement Program database demonstrated increased postoperative morbidity and mortality with the inclusion of venous resection [47]. This difference can be attributed to publication bias since most of the previously published single center studies have been from high-volume centers. Based on this, PD with VR in carefully selected patients at high-volume institutions opens up the possibility of survival comparable to that of patients undergoing standard PD, even in the setting of an increased frequency of R1 resections in patients that require VR [43].

Not only has surgical technique evolved but also, operative standards of care have been improved. It is known that lymph node metastasis is a poor prognostic factor for PDAC of the pancreatic head. The retrieval of an adequate number of lymph nodes or total lymph nodes examined (TNLE) is a measure of quality of care. Not only does it lead to optimal locoregional control but also, it is of upmost importance for pathological staging. Current NCCN guidelines

recommend that at least 11 lymph nodes are retrieved and examined. Gleisner and colleagues showed an association between TNLE and overall survival, but the association was not uniform through time at their institution. Standards of care improved. We have found that less than 12 lymph nodes are inadequate lymphadenectomy [48].

8. Therapeutics

The standard chemotherapy regimen for advanced pancreatic cancer has historically been monotherapy with gemcitabine [49]. In patients with metastatic PDAC, gemcitabine with nab-paclitaxel improved median overall survival (8.5 vs 6.7 months, HR = 0.72, $p < 0.001$), one-year survival (35 vs 22%), two-year survival (9 vs 4%), and improved objective response rate (23 vs 7%) when compared with gemcitabine alone [50]. The most common Grade 3 or higher toxicity events were neutropenia, fatigue, and neuropathy.

Given that the majority of patients who undergo resection with curative intent relapse within 2 years [51], the CONKO-001 trial set to evaluate the efficacy of gemcitabine as adjuvant therapy administered as a dose of 1 g/m^2 on day 1, 8, and 15 every 4 weeks for 6 months. After a median follow-up of 136 months, patients treated with gemcitabine had an increased median disease-free survival (13.4 vs 6.7 months, HR, 0.55 [95% CI, 0.44–0.69]; $p < 0.001$) and prolonged overall survival (HR, 0.76 [95% CI, 0.61–0.95]; $p = 0.01$) versus those patients who were only observed after resection. In 2010, a randomized controlled trial compared the use of fluorouracil plus folinic acid versus gemcitabine as adjuvant chemotherapy. There was no difference in survival between the two treatments [52]. Although alternative chemotherapy regimens have since emerged, utilizing other agents as either monotherapy or in combination with gemcitabine, few studies have demonstrated significantly improved results [24].

There has been increased interest in the use of neoadjuvant therapy for the treatment of pancreatic adenocarcinoma given the potential for better treatment tolerance, improved delivery to an undisturbed tumor bed, avoidance of delay in therapy, treatment of occult micrometastatic disease, and the potential of down staging borderline/unresectable tumors. In a meta-analysis evaluating 14 Phase II trials involving gemcitabine and 5-FU chemotherapy regimens (either as monotherapy or combination therapy), there was no difference in local recurrence between patients who were initially considered resectable prior to systemic therapy and those who were not. Only 1.8% of patients had a complete tumor response, while 18.8% of all patients had partial tumor response based on RECIST criteria or criteria defined by the authors of each respective study. Pathologic response was not reported. While there was no difference in survival between the groups of patients deemed resectable pretreatment and those determined to be unresectable, approximately one-third of tumors initially classified as borderline/unresectable were suitable for resection after neoadjuvant therapy [53].

Despite the lack of Phase III trials addressing neoadjuvant therapy, it is important to emphasize its role in selecting patients who will be good surgical candidates once restaged after completion of treatment. It not only allows for better patient selection based on tumor biology, but

also increases the possibility of R0 resection and patient completion of multimodal therapy. In contrast to the findings described previously, a neoadjuvant approach using gemcitabine-based chemo radiation resulted in a median survival of 34 months for the patients who were candidates for PD versus 7 months for those who did no undergo surgical resection. Additionally, this study revealed that a gemcitabine-based approach to neoadjuvant therapy is superior to 5-FU and paclitaxel-based preoperative regimens in terms of better survival of patients after PD [54].

The FOLFIRINOX regimen, combining 5-flurouracil, leucovorin, irinotecan, and oxaliplatin, was first implemented in the ACCORD-11 trial conducted by the PRODIGE group. Among 342 patients with previously untreated metastatic PDA, this regimen resulted in an increase in median overall survival from 6.8 months in the gemcitabine group to 11.1 months in the FOLFIRINOX group (HR = 0.57, $p < 0.001$). However, the regimen resulted in increased Grade 3 or 4 adverse effects secondary to treatment, such as neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy. The toxicity of the regimen thus raises concern for its use in patients with more advanced age, poor ECOG status, or greater comorbidities. For this group of patients, gemcitabine with nab-paclitaxel may be a better option due to its safer toxicity profile, although response to treatment is not as impressive as that observed with FOLFIRINOX. The efficacy of FOLFIRINOX as first-line therapy in the metastatic setting has prompted the evaluation of its potential in the neoadjuvant setting for patients with borderline or locally advanced disease. FOLFIRINOX followed by chemoradiation as neoadjuvant therapy has been shown to be safe in selected patients and has been shown to result in R0 resections [55]. As FOLFIRINOX continues to become increasingly incorporated into clinical practice, further study of patients who tolerate the regimen will help determine predictive factors associated with improved response to this therapy [56–68].

9. Conclusion

Pancreas adenocarcinoma is an aggressive malignancy. Progression to a multidisciplinary approach to diagnosis, treatment, and perioperative patient management can improve patient outcomes. This can be achieved through the implementation of state-of-the-art diagnostic modalities, including imaging and endoscopic procedures, as well as the application of enhanced recovery pathways that address every aspect of the treatment process from preoperative patient optimization to postoperative rehabilitation. Advances in surgical technique, particularly the use of laparoscopy and robotic-assisted surgery, also provide benefits to patients without compromising oncologic outcomes. Lastly, advancements in systemic chemotherapy, although slower in progression, have shown some improvement in survival when combined with surgical resection and offer a treatment alternative to patients with advanced disease who are not surgical candidates.

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References

[1] Rahib, L., B. D. Smith, R. Aizenberg, A. B. Rosenzweig, J. M. Fleshman, and L. M. Matrisian. "Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States." Cancer Research 74.11 (2014): 2913–921.

[2] Ma, J., R. Siegel, and A. Jemal. "Pancreatic Cancer Death Rates by Race Among US Men and Women, 1970-2009." JNCI Journal of the National Cancer Institute 105.22 (2013): 1694–700.

[3] Winter, J. M., M. F. Brennan, L. H. Tang, M. I. D'Angelica, R. P. Dematteo, Y. Fong, D. S. Klimstra, W. R. Jarnagin, and P. J. Allen. "Survival after Resection of Pancreatic Adenocarcinoma: Results from a Single Institution over Three Decades." Annals of Surgical Oncology Ann Surg Oncol 19.1 (2011): 169–75.

[4] Thorson, Alan G. "Progress in Cancer Care: A Rational Call To Do Better." CA: A Cancer Journal for Clinicians 60.1 (2010): 7–11.

[5] Riall, T., W. Nealon, J. Goodwin, D. Zhang, Y. Kuo, C. Townsendjr, and J. Freeman. "Pancreatic Cancer in the General Population: Improvements in Survival Over the Last Decade." Journal of Gastrointestinal Surgery 10.9 (2006): 1212–224.

[6] Bilimoria, K. Y., D. J. Bentrem, C. Y. Ko, A. K. Stewart, D. P. Winchester, and M. S. Talamonti. "National Failure to Operate on Early Stage Pancreatic Cancer." Annals of Surgery 246.2 (2007): 173–180.

[7] Schiffman, S. C., S. Abberbock, S. Winters, C. Valko, J. Steve, A. H. Zureikat, H. J. Zeh, and M. E. Hogg. "A Pancreatic Cancer Multidisciplinary Clinic: Insights and Outcomes." Journal of Surgical Research 202.2 (2016): 246–52.

[8] Pawlik, T. M., D. Laheru, R. H. Hruban, J. Coleman, C. L. Wolfgang, K. Campbell, S. Ali, E. K. Fishman, R. D. Schulick, and J. M. Herman. "Evaluating the Impact of a Single-Day Multidisciplinary Clinic on the Management of Pancreatic Cancer." Annals of Surgical Oncology 15.8 (2008): 2081–088.

[9] Gardner, T. B., R. J. Barth, B. I. Zaki, B. R. Boulay, M. M. Mcgowan, J. E. Sutton, G. H. Ripple, T. A. Colacchio, K. D. Smith, I. R. Byock, M. Call, A. A. Suriawinata, M. J.

Tsapakos, J. B. Mills, A. Srivastava, M. Stannard, M. Lisovsky, S. R. Gordon, and J. M. Pipas. "Effect of Initiating a Multidisciplinary Care Clinic on Access and Time to Treatment in Patients with Pancreatic Adenocarcinoma." Journal of Oncology Practice 6.6 (2010): 288–92.

[10] Katz, M. H. G., H. Wang, J. B. Fleming, C. C. Sun, R. F. Hwang, R. A. Wolff, G. Varadhachary, J. L. Abbruzzese, C. H. Crane, S. Krishnan, J.-N. Vauthey, E. K. Abdalla, J. E. Lee, P. W. T. Pisters, and D. B. Evans. "Long-Term Survival After Multidisciplinary Management of Resected Pancreatic Adenocarcinoma." Annals of Surgical Oncology 16.4 (2009): 836–47.

[11] Wray, C. J., E. Castro-Echeverry, E. J. Silberfein, T. C. Ko, and L. S. Kao. "A Multi-institutional Study of Pancreatic Cancer in Harris County, Texas: Race Predicts Treatment and Survival." Annals of Surgical Oncology 19.9 (2012): 2776–781.

[12] Khawja, S. N., S. Mohammed, E. J. Silberfein, B. L. Musher, W. E. Fisher, and G. Van Buren. "Pancreatic Cancer Disparities in African Americans." Pancreas 44.4 (2015): 522–27.

[13] Fisher, W. E., S. E. Hodges, M.-F. Wu, S. G. Hilsenbeck, and F. C. Brunicardi. "Assessment of the Learning Curve for Pancreaticoduodenectomy." The American Journal of Surgery 203.6 (2012): 684–90.

[14] Evans, D. B., G. R. Varadhachary, C. H. Crane, C. C. Sun, J. E. Lee, P. W. T. Pisters, J.-N. Vauthey, H. Wang, K. R. Cleary, G. A. Staerkel, C. Charnsangavej, E. A. Lano, L. Ho, R. Lenzi, J. L. Abbruzzese, and R. A. Wolff. "Preoperative Gemcitabine-Based Chemoradiation for Patients with Resectable Adenocarcinoma of the Pancreatic Head." Journal of Clinical Oncology 26.21 (2008): 3496–502.

[15] Oettle, H., P. Neuhaus, A. Hochhaus, J. T. Hartmann, K. Gellert, K. Ridwelski, M. Niedergethmann, C. Zülke, J. Fahlke, M. B. Arning, M. Sinn, A. Hinke, and H. Riess. "Adjuvant Chemotherapy with Gemcitabine and Long-term Outcomes Among Patients With Resected Pancreatic Cancer." JAMA 310.14 (2013): 1473.

[16] King, J. C., M. Zenati, J. Steve, S. B. Winters, D. L. Bartlett, A. H. Zureikat, H. J. Zeh, and M. E. Hogg. "Deviations from Expected Treatment of Pancreatic Cancer in Octogenarians: Analysis of Patient and Surgeon Factors." Annals of Surgical Oncology (2016).

[17] "Further Evidence of Effective Adjuvant Combined Radiation and Chemotherapy following Curative Resection of Pancreatic Cancer." Cancer 59.12 (1987): 2006–010.

[18] Lee, E. S. "Imaging Diagnosis of Pancreatic Cancer: A State-of-the-Art Review." World Journal of Gastroenterology 20.24 (2014): 7864.

[19] Gurusamy, K. S., and B. R. Davidson. "Diagnostic Accuracy of Different Imaging Modalities following Computed Tomography (CT) Scanning for Assessing the Resectability with Curative Intent in Pancreatic and Periampullary Cancer." Protocols Cochrane Database of Systematic Reviews (2015).

[20] Karmazanovsky, G., V. Fedorov, V. Kubyshkin, and A. Kotchatkov. "Pancreatic Head Cancer: Accuracy of CT in Determination of Resectability." Abdominal Imaging 30.4 (2005): 488–500.

[21] Shrikhande, S. V., S. G. Barreto, M. Goel, and S. Arya. "Multimodality Imaging of Pancreatic Ductal Adenocarcinoma: A Review of the Literature." HPB 14.10 (2012): 658–68.

[22] Callery, M. P., K. J. Chang, E. K. Fishman, M. S. Talamonti, L. W. Traverso, and D. C. Linehan. "Pretreatment Assessment of Resectable and Borderline Resectable Pancreatic Cancer: Expert Consensus Statement." Annals of Surgical Oncology 16.7 (2009): 1727–733.

[23] Mohammed, S., and W. E. Fisher. "Quality Metrics in Pancreatic Surgery." Surgical Clinics of North America 93.3 (2013): 693–709.

[24] Mohammed, S., G. Van Buren, II, and W. E. Fisher. "Pancreatic Cancer: Advances in Treatment." World Journal of Gastroenterology 20.28 (2014): 9354–360 (in print).

[25] Finks, J. F., N. H. Osborne, and J. D. Birkmeyer. "Trends in Hospital Volume and Operative Mortality for High-Risk Surgery." New England Journal of Medicine 364.22 (2011): 2128–137.

[26] Tseng, J., C. Raut, J. Lee, P. Pisters, J. Vauthey, E. Abdalla, H. Gomez, C. Sun, C. Crane, and R. Wolff. "Pancreaticoduodenectomy with Vascular Resection: Margin Status and Survival Duration." Journal of Gastrointestinal Surgery 8.8 (2004): 935–50.

[27] Katz, M. H. G., P. W. T. Pisters, D. B. Evans, C. C. Sun, J. E. Lee, J. B. Fleming, J. N. Vauthey, E. K. Abdalla, C. H. Crane, R. A. Wolff, G. R. Varadhachary, and R. F. Hwang. "Borderline Resectable Pancreatic Cancer: The Importance of This Emerging Stage of Disease." Journal of the American College of Surgeons 206.5 (2008): 833–46.

[28] Lassen, K., M. M. E. Coolsen, K. Slim, F. Carli, J. E. De Aguilar-Nascimento, M. Schäfer, R. W. Parks, K. C. H. Fearon, D. N. Lobo, N. Demartines, M. Braga, O. Ljungqvist, and C. H. C. Dejong. "Guidelines for Perioperative Care for Pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society Recommendations." World Journal of Surgery 37.2 (2012): 240–58.

[29] Halaszynski, T. M., R. Juda, and D. G. Silverman. "Optimizing Postoperative Outcomes with Efficient Preoperative Assessment and Management." Critical Care Medicine 32.Supplement (2004).

[30] Bratzler, D. W., E. P. Dellinger, K. M. Olsen, T. M. Perl, P. G. Auwaerter, M. K. Bolon, D. N. Fish, L. M. Napolitano, R. G. Sawyer, D. Slain, J. P. Steinberg, and R. A. Weinstein. "Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery." American Journal of Health-System Pharmacy 70.3 (2013): 195–283.

[31] Eshuis, W. J., J. Hermanides, J. W. Van Dalen, G. Van Samkar, O. R.C. Busch, T. M. Van Gulik, J. H. Devries, J. B.l. Hoekstra, and D. J. Gouma. "Early Postoperative Hypergly-

cemia Is Associated With Postoperative Complications After Pancreatoduodenectomy." Annals of Surgery 253.4 (2011): 739–44.

[32] Kehlet, H., and D. W. Wilmore. "Multimodal Strategies to Improve Surgical Outcome." The American Journal of Surgery 183.6 (2002): 630–41.

[33] Fisher, W.E., S. Hodges, G. Cruz, et al. "Routine Nasogastric Suction May Be Unnecessary After a Pancreatic Resection." HPB 13 (2011): 792–796.

[34] Balzano, G., A. Zerbi, M. Braga, et al. "Fast-track Recovery Programme after Pancreaticoduodenectomy Reduces Delayed Gastric Emptying." British Journal of Surgery 95 (2008): 1387–93.

[35] Buren, G. Van, M. Bloomston, S. J. Hughes, J. Winter, S. W. Behrman, N. J. Zyromski, C. Vollmer, V. Velanovich, T. Riall, P. Muscarella, J. Trevino, A. Nakeeb, C. M. Schmidt, K. Behrns, E. C. Ellison, O. Barakat, K. A. Perry, J. Drebin, M. House, S. Abdel-Misih, E. J. Silberfein, S. Goldin, K. Brown, S. Mohammed, S. E. Hodges, A. Mcelhany, M. Issazadeh, E. Jo, Q. Mo, and W. E. Fisher. "A Randomized Prospective Multicenter Trial of Pancreaticoduodenectomy With and Without Routine Intraperitoneal Drainage." Annals of Surgery 259.4 (2014): 605–12.

[36] Sharpe, S.M., M.S. Talamonti, C.E. Wang, et al. "Early National Experience with Laparoscopic Pancreaticoduodenectomy for Ductal Adenocarcinoma: A Comparison of Laparoscopic Pancreaticoduodenectomy and Open Pancreaticoduodenectomy from the National Cancer Data Base." Journal of the American College Surgery 221 (2015): 175–184.

[37] Lee, S., P. Allen, E. Sadot, et al. "Distal Pancreatectomy: A Single Institution's Experience in Open, Laparoscopic, and Robotic Approaches." Journal of the American College of Surgery 220.1 (2014): 18–27.

[38] Kooby, D., T. Gillespie, D. Bentrem et al. "Left-sided Pancreatectomy: A Multicenter Comparison of Laparoscopic and Open Approaches." Annals of Surgery; 248.3 (2008).

[39] Zureikat, A., L. Postlewait, Y. Liu, et al. (2016). "A Multi-instititional Comparison of Perioperative Outcomes of Robotic and Open Pancreaticoduodenectomy." Annals of Surgery. (In print).

[40] Waters, J.A., D.F. Canal, E.A. Wiebke, et al. (2010). "Robotic Distal Pancreatectomy: Cost Effective?" Surgery 148 (2010): 814–823.

[41] Geller, E.J., and C.A. Matthews,. "Impact of Robotic Operative Efficiency on Profitability." American Journal of Obstetrics Gynecology 211.5 (2013): 546.

[42] Wright, G.P., A. Zureikat,. "Development of Minimally Invasive Pancreatic Surgery: An Evidence-Based Systematic Review of Laparoscopic Versus Robotic Approaches." Journal of Gastrointestinal Surgery 20.9 (2016): 1658–65.

[43] Tseng, J., C. Raut, andJ. Lee,. "Pancreaticoduodenectomy with Vascular Resection: Margin Status and Survival Duration." Journal of Gastrointestinal Surgery 8.8 (2004): 935–950.

[44] Christians, K., and D.B. Evans,. "Pancreaticoduodenectomy and Vascular Resection: Persistent Controversy and Current Recommendations." Annals of Surgical Oncology 16 (2009): 789–91.

[45] Ramacciato, G., P. Mercantini, N. Petrucciani, et al. "Does Portal-superior Mesenteric Vein Invasion still Indicate Irresectability for Pancreatic Carcinoma?" Annals of Surgical Oncology; 16 (2009): 817–825.

[46] Fuhrman, G.M., S.D. Leach, C.A. Staley, et al. "Rationale for en bloc Vein Resection in the Treatment of Pancreatic Adenocarcinoma Adherent to the Superior Mesenteric-Portal Vein Confluence." Pancreatic Tumor Study Group. Annals of Surgery; 223 (1996): 154–162.

[47] Castleberry, A., R. White, S. De La Fuente, et al. "The Impact Vascular Resection on Early Postoperative Outcomes after Pancreaticoduodenectomy: An Analysis of the American College of Surgeons National Surgical Quality Improvement Program Database." Annals of Surgical Oncology; 19 (2012): 4068–4077.

[48] Gleisner, A., G. Spolverato, A. Ejaz, and T. Pawlik. "Time-related Changes in the Prognostic Significance of the Total Number of Examined Lymph Nodes in Node-negative Pancreatic Head Cancer." Journal of Surgical Oncology; 110.7 (2014): 858–63.

[49] Burris, H,, M. Moore, and J. Andersen. "Improvements in Survival and Clinical Benefit with Gemcitabine as First-Line Therapy for Patients with Advanced Pancreas Cancer: A Randomized Trial." Journal of Clinical Oncology; 15.6 (1997): 2403–2413.

[50] Von Hoff, D., T. Ervin, F. Arena, et al.. "Increased Survival in Pancreatic Cancer with Nab-placlitaxel Plus Gemcitabine." NEJM; 369.18 (2013): 1691–1703.

[51] Sener, S.F., A. Fremgen, H.R. Menck, and D.P. Winchester, "Pancreatic Cancer: A Report of Treatment and Survival Trends for 100,313 Patients Diagnosed from 1985–1995, using the National Cancer Database." *J Am Coll Surg*.189.1 (1999): 1–7.

[52] Neoptolemos, J., D. Stocken, C. Bassi, et al. "Adjuvant Chemotherapy with Fluorouracil plus Folinic Acid vs Gemcitabine Following Pancreatic Cancer Resection: A Randomized Controlled Trial." JAMA; 304.10 (2010): 1073–1081.

[53] Assifi, M,, X. Lu, G. Eibl, et al. "Neoadjuvant Therapy in Pancreatic Adenocarcinoma: A Meta-analysis of Phase II Trials." Surgery 150.3 (2011): 466–473.

[54] Evans, D., G. Varadhchary, C. Crane, et al. "Preoperative Gemcitabine-based Chemoradiation for Patients with Resectable Adenocarcinoma of the Pancreatic Head." Journal of Clinical Oncology; 26.21 (2008): 3496–3502.

[55] Christians, K,, S. Tsai, A. Mahmoud, et al. "Neoadjuvant FOLFIRINOX for Borderline Resectable Pancreas Cancer: A New Treatment Paradigm?" The Oncologist 19 (2014).: 266–274.

[56] Xiong, J., P. Szatmary, B. Chir, et al. "Enhanced Recovery after Surgery Program in Patients undergoing Pancreaticoduodenectomy: A PRISMA-Compliant Systematic Review and Meta-analysis." Medicine 95.18 (2016): 1–10.

[57] Adham, M., X. Chopin-Laly, and V. Lepilliez, et al. "Pancreatic Resection: Drain or No Drain?" Surgery 154.5 (2013): 1069–77.

[58] Conlon, K., D. Labow, D. Leung, et al. "Prospective Randomized Clinical Trial of the Value of Intraperitoneal Drainage after Pancreatic Resection." Annals of Surgery 234 (2001): 487–494.

[59] Correa-Gallego, C., M. Brennan, M. D'Angelica, et al. "Operative Drainage Following Pancreatic Resection: Analysis of 1122 Patients Resected over 5 years at a Single Institution." Annals of Surgery 258 (2013): 1051–1058.

[60] Fisher, W.E., S. Hodges, E. Silberfein, et al. "Pancreatic Resection without Routine Intraperitoneal Drainage." HPB 13 (2011): 503–510.

[61] Heslin, M., L. Harrison, A. Brooks, et al. "Is Intra-abdominal Drainage Necessary after Pancreaticoduodenectomy?" Journal of Gastrointestinal Surgery 2 (1998): 373–378.

[62] Bilimoria, K., J. Bentrem, and C. Ko, et al. "National Failure to Operate on Early Stage Pancreatic Cancer." Annals of Surgery 246.2 (2007): 173–180.

[63] Reber, H.A.. "Lymph Node Involvement as a Prognostic Factor in Pancreatic Cancer." International Journal of Pancreatology 7 (1990):125–127.

[64] Huebner, M., M. Kendrick, K.M. Reid-Lombardo, et al. "Number of Lymph Nodes Evaluated: Prognostic Value in Pancreatic Adenocarcinoma." Journal of Gastrointestinal Surgery 16 (2012): 920–926.

[65] Oettle, H., S. Post, P. Neuhaus, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 297.3 (2007): 267–277.

[66] Oettle, H., P. Neuhaus, and A. Hochhaus, "Adjuvant Chemotherapy with Gemcitabine and Long-term Outcomes among Patients with Resected Pancreatic Cancer: The CONKO-001 Randomized Trial." JAMA 310.14 (2013): 1473–1481.

[67] Therasse, P., S.G. Arbuck, E.A. Eisenhauer, J. Wander, Kaplan, et al. "New Guidelines to Evaluate the Response to Treatment in Solid Tumors." Journal of National Cancer Institute 92 (2000): 205–16.

[68] Evans, D.B., T.A. Rich, D.R. Byrd, et al. "Preoperative Chemoradiation and PD for Adenocarcinoma of the Pancreas." Archives of Surgery 127 (1992): 1335–1339.

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