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Redefining the Scalpel: Past, Present, and Future Perspectives on the Surgical Management of Pancreatic Ductal Adenocarcinoma (PDAC)

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Abstract

PDAC is still one of the most lethal cancer challenges, since it is characterized by an aggressive biology, early systemic dissemination, and a historically dismal prognosis. For many years, surgical resection has been considered the only potential treatment modality. However, the role, performance, extent, and opportunity of pancreatectomy (either distal or pancreatoduodenectomy) have undergone a significant paradigm shift. This manuscript traces the evolution of PDAC surgery from its dawn to a highly standardized procedure in high-volume centers.

In the current era, the therapeutic paradigm has predominantly shifted from a "surgery-first" approach to an aggressive multidisciplinary approach, where advanced systemic neoadjuvant regimens and minimally invasive (laparoscopic/robotic) approaches are systematically used to achieve R0 resection. The future will likely overcome macro- and micro-anatomical boundaries through the full integration of artificial intelligence (AI), radiomics, molecular margin assessment, intraoperative navigation, and personalized immunotherapies. In that fashion, the pancreatic surgeon will need to transition from technician to biological oncologist, and his/her scalpel will transform into a bridge toward systemic disease eradication.

Key Points

- **Question:** How has the role of surgical resection for PDAC evolved through different stages and landscapes?

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- **Findings:** The field has shifted from high mortality and few resections to safer, mostly centralized interventions. Neoadjuvant therapy, vascular resections, and minimally invasive (laparoscopic and robotic) platforms characterize the present. The future will integrate artificial intelligence-aided resources, real-time fluorescence-guided molecular margins, and personalized post-operative mRNA vaccines.
- **Meaning:** surgical management of PDAC has shifted from a focus on macro-anatomical technical feasibility to a biology-driven, technologically integrated component of personalized oncologic treatment.

Introduction

Pancreatic adenocarcinoma (PDAC) continues to show a rising incidence worldwide, representing the fourth leading cause of cancer death in Western countries, with a five-year survival rate of 5% to 12%[1]. It is the most common histological type, accounting for about 85% to 90% of pancreatic malignancies. Fewer than 15% are considered resectable at the time of diagnosis[2]. The pancreas was first described by Herophilus of Chalcedon (335 BC–280 BC), and the term pancreas ("all flesh") was coined by Rufus of Ephesus (70-110). Giovanni Battista Morgagni (1682-1771) is credited with the earliest recorded accounts of pancreatic ductal adenocarcinoma (PDAC), as he reported several cases of pancreatic "scirrhus" in his 1761 publication "The seats and causes of diseases"[3].

The past

The history and development of pancreatic surgery was characterized by anatomical and physiological hindrances. The gland's location, its relationship with major visceral vessels, and the corrosive nature of its exocrine secretions made any operative manipulation extremely hazardous. This explains the disastrous outcomes, either due to intraoperative and, most of the time, uncontrollable bleeding or lethal post-operative complications (usually pancreatic fistulas).

The surgical treatment of PDAC underwent several stages: the first one was in the period 1880-1905, represented by bypass operations to alleviate the obstruction and palliate the jaundice. In 1887, almost simultaneously, Otto Kappeler in Munsterlingen, Switzerland, and Nestor Monastyrski in Russia performed the first cholecystojejunostomies for biliary obstruction caused by pancreatic carcinoma[4,5]. However, Kappeler was the first to report it[6]. In both cases, the patient survived the operation. Swiss surgeon Cesar Roux's major contribution was describing the Roux-en-Y anastomosis, which forms the backbone of modern reconstructions after pancreatoduodenectomy (PD)[7]. Ambroise Monprofit (1857-1922) was the first one to perform the Roux-en-Y technique in a cholecystojejunostomy in 1904[8].

The second stage is focused on the initial resections of the pancreatic tail. Between 1882 and 1905, 21 surgeons performed 24 resections[3]. Although these patients were not jaundiced, no intestinal resection was needed, and arterial bleeding was easier to control; only half of the patients were able to be discharged from hospitals. The third stage involved developing and achieving peri-ampullary carcinoma resection in two steps: Alessandro Codivilla in Bologna, Italy, and William Halsted in Baltimore, USA, performed the first cases in 1898. Walter Kausch performed a successful partial PD in Berlin. In 1933, at Columbia University in New York, Allen Whipple and his team performed what is considered the modern PD[9,10]. Whipple's milestone demonstrated that "en bloc" resection of the pancreatic head, duodenum, distal stomach, and common bile duct was anatomically feasible and compatible with life, although characterized by high morbidity and mortality. Meanwhile, Isaac Trimble from Johns Hopkins also performed pancreatoduodenectomies, apparently earlier than Whipple but published his results later[11]. Many years later, Traverso proposed the pylorus-preserving pancreatoduodenectomy to prevent delayed gastric emptying[12]. Notably, Henrik Dam discovered vitamin K in 1929 (1943 Nobel Prize), and it has been available since 1939, which was crucial because many PDAC patients had clotting disorders.

The burden of a steep mortality kept this procedure dangerous for several decades after its inception. These outcomes and the lack of effective systemic chemotherapy for the treatment of PDAC meant long-term survival was limited. Thus, many questioned the ethical and clinical utility and validity of the Whipple procedure. In more recent times, the PD has been linked to the figure of John L Cameron, from Johns Hopkins, who achieved some of the best surgical outcomes worldwide in the treatment of PDAC[13].

The turning point that saved pancreatic surgery from dismal results and rejection took place in the late '80s and '90s with the revolution of clinical centralization, when epidemiological studies revealed an undeniable volume-outcome relationship in pancreatic resections. Centralization shifted complex pancreatic surgery into specialized regional centers hosting multidisciplinary teams of excellence (outstanding pancreatic surgeons, dedicated anesthesia teams, interventional radiologists capable of managing complications percutaneously, intensivists and top nursing

staff). These changes reduced perioperative mortality from over 20% to under 5% in high-volume centers and were associated with better oncological outcomes[14].

The present

Three paradigm shifts characterize the current treatment of PDAC. They are represented by multidisciplinary team synergy, the shift from surgery-first to neoadjuvant therapy, and minimally invasive access with extended vascular resections. As mentioned before, centralization led to the formation of multidisciplinary teams whose achievements improve clinical outcomes (both perioperative and oncological).[15]

For decades, the standard clinical approach was upfront surgery for those with PDAC considered resectable, followed by adjuvant chemotherapy. However, this "surgery-first" strategy presented significant limitations: 30% of patients undergoing the procedure were found to have positive microscopic margins (R1), and a substantial proportion of patients presented with early and rapid systemic recurrence within months of surgery, an indication that occult micrometastatic disease was present at the time of operation. Moreover, postoperative complications often delayed or precluded the timely initiation of chemotherapy. The introduction and widespread adoption of neoadjuvant systemic chemotherapy, most notably FOLFIRINOX or Gemcitabine plus Paclitaxel, revolutionized patient care. The neoadjuvant approach presents several advantages: early systemic treatment, tumor biology assessment, tumor downstaging, and improved adjuvant compliance.[16]

Early efforts in the '90s to introduce laparoscopic techniques for pancreatic surgery were met with skepticism because of the procedure's inherent technical challenges, including complex anastomoses and extended operative times. These concerns contributed to the delayed adoption of minimally invasive pancreatic resection, which did not gain broader clinical traction until the initial years of this century, with the appraisal of robotic approaches. Currently, Whipple procedures are predominantly performed through an open incision, with minimally invasive PD representing about 10.52% of the cases, 62% robotic and 38% laparoscopic[17]. Notably, the resection rate doubled from 8.3% to 16.6%, with improved survival[18].

This era is also characterized by the rise of minimally invasive and robotic platforms, driven by technological innovation in the technical execution of pancreatectomies, both distal and proximal. For tumors located in the pancreatic body and tail, laparoscopic or robotic-assisted distal pancreatectomy with splenectomy has become the standard approach in many centers, offering equivalent oncological outcomes with significantly reduced postoperative pain, shorter hospital stays, and faster recovery times[19]. More recently, robotic platforms have made substantial contributions to performing the Whipple procedure, overcoming the inherent limitations of conventional laparoscopy by providing 3-D vision, wristed instrumentation, tremor filtration, and navigation aids. These features are particularly beneficial during the complex suturing phases of pancreatojejunostomy and hepaticojejunostomy. Robotic platforms have demonstrated equivalent safety and margin clearance when performed by experts, and patients benefit from quicker recovery periods[20].

Another aspect of resections is advanced vascular reconstruction, as resectability has evolved from rigid anatomical standards to dynamic, boundary-pushing endeavors. Historically, tumor involvement of major retroperitoneal vessels (superior mesenteric artery, superior mesenteric vein, portal vein or celiac axis) was considered an absolute contraindication. Today, pancreatic surgeons at high-volume centers routinely perform planned, complex vascular reconstructions. After neoadjuvant downstaging, involvement of vascular structures is no longer an impediment to pancreatic resection[21].

The future

Most probably, the future of pancreatic surgery will lie at the intersection of advanced technology, molecular biology, immunotherapy, and artificial intelligence[22–23].

- Total robotic integration will allow autonomous robotic steps under the surgeon's supervision, assisted by real-time navigation mapping major retroperitoneal vessels and maximizing patient safety.
- Fluorescence-guided surgery: tumor-specific dyes will aid visualization and real-time assessment of tumor margins and positive lymph nodes.
- The concept of "clear margins" will likely shift from metric dimensions (1 mm) to biological dimensions, using intraoperative rapid genetic sequencing.
- Artificial intelligence and radiomics: preoperative machine learning algorithms will predict microvascular involvement and allow improved patient selection for resection. Besides, the operating rooms of the future will offer an immersive, digitally augmented environment.
- Personalized vaccines: postoperative care will include customized mRNA vaccines and/or targeted immunotherapies tailored to the genetic profile of the patient's tumor[24].

Probably the most important conceptual transformation

of the future is that the surgical scalpel will no longer be considered the definitive and standard cure for PDAC. Surgery will probably evolve into a coordinated biological bridge within a personalized immunotherapy framework. The surgical specimen will serve as a valuable biobank, allowing the identification of neo-antigens and the development of specific mRNA vaccines or T-cell therapies[25].

In conclusion, the surgical treatment of PDAC has undergone a remarkable evolution since its initial stages. The past established the foundations and principles of the procedure, the present transformed surgery into a multi-modality systemic tapestry, while the future promises a complete departure from pure anatomical surgery. As the field continues to evolve, the modern pancreatic surgical oncologist must look beyond the physical boundaries of the scalpel, embracing technology and tumor biology to finally lead the war against this devastating disease.

We would like to close these reflections with the following quote: "In the world of surgical oncology, Biology is King, selection is queen, technical maneuvers are the Prince and Princess. Occasionally the prince or princess tries to usurp the throne; they almost fail to overcome the powerful forces of the King and Queen"[26].

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