Clinics of Surgery

Review Article

ISSN 2638-1451 | Volume 5

Evolution of Pancreatic Cancer Management

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Received: 15 June 2021
Accepted: 05 July 2021
Published: 12 July 2021

Keywords:

Pancreatic adenocarcinoma; Pancreatic surgery; Systemic therapies; Neo-adjuvant treatment

Citation:

Abdelkader B, et al., Evolution of Pancreatic Cancer Management. Clin Surg. 2021; 5(14): 1-5

1. Abstract

Despite the advanced progress made in treating pancreatic cancer including surgical technique refinement and improvement of adjuvant and neo-adjuvant therapies, the pancreatic adenocarcinoma has doubled incidence during the last decades and it remains the most aggressive tumor with low long-term survival rate and poor quality of life. This review aims to provide an overview of the evolution of the management of pancreatic cancer and highlight the importance of future research focus on the development of strategies for prevention and early diagnosis, and identification of more effective systemic treatments to improve long-term survival and quality of life.

2. Introduction

Rising from exocrine pancreas, the adenocarcinoma remains the most common and aggressive tumour with doubling incidence during the last three decades [1]. Additionally, the adenocarcinoma has globally become the 7th related death cause in 2018 [2]. Currently, pancreatic adenocarcinoma has become the leading cause of cancer-related mortality in the USA [3]. The surgical and medical management of pancreatic malignancy has dramatically evolved and initially fatal, this disease is today more curable. This review aims to highlight pancreatic cancer management evolution including early diagnosis, surgical techniques and systemic therapies.

3. Evolution of Cancer Pancreatic Surgery

The surgery remains the main treatment of the non-metastatic pancreatic cancer.

Since the first pancreatic resection performed in 1882 [4], The pancreatic surgery has substantially evolved, over the past decades. The first two-stage complete pancreaticoduodenectomy had been achieved by Allen Whipple, from Columbia-Presbyterian Medical Center-USA, in 1935 [5]. The first stage of procedure consisted of performing gastroenterostomy, ligation of the common bile duct and cholecystogastrostomy. The duodenum resection and the pancreatic head excision were performed in the second stage of the operation.

Seven years later (1942), the same author (Whipple) completed the operation in one stage including distal gastrectomy, entire resection of the duodenum and the pancreatic head [6]. The reconstruction was achieved by performing gastrojejunostomy and choledochojejunostomy. Furthermore, pancreaticojejunostomy had been added to the procedure [7]. At the end of the 1960s, the high operative mortality (>30%) and the poor long-term survival (0 - 5%) following pancreaticoduodenectomy has led to question the curative versus palliative nature of this surgical procedure [8, 9]. Over time, the improvement of the surgical technique including shortened operative time and reduced blood loss, resulted in substantial reduced mortality. The centralization of management at high volume centers and remarked progress made in imaging, interventional radiology, critical care and anesthetic techniques had led to improving postoperative outcomes and reducing operative mortality. Importantly, the association of improved outcomes with high surgical volume centres has been clearly demonstrated [10-12]. The centralization of care allowed the better selection of patients, improving the learning curve and acquisition of surgical skills, early diagnosis and appropriate management of postoperative complications. Indeed, the current reported operative mortal-

ity following pancreaticoduodenectomy was less than 3% at high volume centres [13]. Currently, the pancreatic surgery is feasible, safe and effective as a treatment option for pancreatic cancer. Despite the increased improvement of the postoperative mortality, pancreaticoduodenectomy remains a high-risk surgical procedure with a morbidity ranging from 40 to 50%. The pancreatic fistula. Remains the most common complication and leading cause of mortality.

Over time, the surgical techniques have been substantially improved. The minimally invasive surgery including robotic and laparoscopic approaches has gained acceptance among the surgical community. The international evidence-based guidelines recommend minimally invasive distal pancreatectomy over open surgery for benign and low-grade malignant tumors of the distal pancreas [14]. Compared to open surgery, minimally invasive distal pancreatectomy was safe and associated with early functional recovery, better quality of life and shorter hospital stay [15, 16]. Whereas, overall complication rate was similar for both procedures. Additionally, ongoing and further randomized trials will provide a highly quality evidence on the minimally invasive distal pancreatectomy, regarding the postoperative outcomes and quality of life [14].

As reported by large retrospective studies, when performed in high -volume centres, robotic and laparoscopic pancreaticoduodenectoy is safe and associated with equivalent mortality, morbidity and oncologic outcomes, compared to open surgery, and when performed in high -volume centres [17-20]. However, more consistent large trials are highly needed to accurately evaluate mortality, morbidity, oncologic outcomes and quality of life following minimally invasive pancreaticoduodenectoy.

4. Systemic Therapies and Survival Improvement

Compared to observation, the significant survival benefit of adjuvant chemo-radiotherapy for resected patients had been demonstrated by the published randomized trials with substantial increase of median Overall Survival (OS).

The use of an adjuvant multi-agent regimen has improved the long-term survival of patients with pancreatic cancer. Currently, modified FOLFIRINOX (fluoruracil, leucovorin, irinotecan, and oxaliplatin), gemcitabine and capecitabine is the standard adjuvant therapy option. Compared to gemcitabine, the modified FOLFIRINOX was recently associated with significant improvement of mediane disease–free survival (21.6 months' vs 12.8 months) [21]. Additionally, the modified 'FOLFIRINOX' is the most used adjuvant therapy option after pancreatic cancer surgery and it is becoming the standard in many centres. A six months of adjuvant systemic therapy had been recommended for resected patients who did not receive preoperative therapy]. The potential benefits of the neo-adjuvant therapy include increase of surgical resection rate of locally advanced cancer, early control of systemic disease dissemination. Actually, preoperative therapy is recommended for borderline resected pancreatic tumours with suspected vascular involvement showed by radiographic finding. Also, neo-adjuvant therapy is indicated in case of increased serum level of CA 19–9, suggestive of disseminated disease [22]. The research efforts focused on the development of neo-adjuvant therapy in treating pancreatic cancer. The benefits of neo-adjuvant therapy for pancreatic cancer have been highlighted by randomized trials. The Dutch phase III randomized trial (PREOPANC) has compared surgery first for resectable and borderline resectable pancreatic cancer with neo-adjuvant chemotherapy using gemcitabine followed by chemoradiotherapy (gemcitabine) and surgery. The surgical procedure consisted of performing a pancreatic-oduodenectomy. The significant benefits on disease–free survival, R0 resection rate, and lower rates of Perineural invasion, metastatic lymph nodes, and venous invasion have been clearly showed, however, there was no significant difference in term of overall survival [24]. The Japanese phase II/III randomized trial (prep-02/JSAP-05) compared preoperative chemotherapy using gemcitabine and S-1 followed by surgery and adjuvant S-1, with surgery followed by adjuvant S-1 [25]. The results revealed a significant median overall survival (36.7 months' vs 26.6 months) associated with the neo-adjuvant gemcitabine and S-1. However, resection rate, Ro resection, and perioperative complications were similar in both groups without statistical difference. So, the optimized use of adjuvant chemotherapy and chemo-radiotherapy has resulted in prolonged median OS for resected pancreatic cancer. However, the long-term survival rate remains very low. The pancreatic cancer showed a poor rate response to immune checkpoint therapies partly linked to the abundant desmoplastic stroma that leads to impairing drug delivery and creating an immunosuppressive microenvironment [26, 27]. The ongoing research targeting the desmoplastic stroma is promising in developing new immune checkpoint and stroma directed therapies [28].

5. Further Perspectives

The ongoing efforts should focus on the early diagnosis, prevention and molecule understanding of the pancreatic cancer in order to improve outcomes, overall survival and quality of life. The frequent late clinical presentation of the pancreatic cancer resulting in delayed diagnosis where surgery is no longer possible and the continuous rise of the global incidence should prompt the importance of prevention and early diagnosis [1]. The risk factors for pancreatic caner include smoking, obesity, chronic pancreatitis and diabetes [29, 30]. Hereditary pancreatic cancer accounts about 5–10% of cases. The hereditary risk factors include multiple hereditary tumor syndromes, hereditary pancreatitis, and familial pancreatic cancer [30, 32, 33]. Well defined, the precursor lesions include Pancreatic Intraepithelial Neoplasia (PanIN), Intra-Ductal Papillary Mucinous Neoplasm (IPMN), and Mucinous Cystic Neoplasm (MCN) [33]. The management guidelines of the IPMN and MCN lesions have been clearly outlined [34, 35].

The high-risk individuals should be screened for early detection of pancreatic cancer and improvement of survival. As recommended by the International Cancer of the Pancreas Screening (CAPS) Consortium, surveillance of individuals with familiar risk should be started at age of 50-55 years or 10 years earlier when a pancreatic cancer was diagnosed in the youngest high-risk individual. The surveillance program includes endoscopic ultrasound, Magnetic Resonance Imaging (MRI) and Magnetic Resonance Cholangio Pancreatography (MRCP) [36]. These tests were associated with high rate of detection and re-secability (75-90%) [37, 38]. The glycan carbohydrate antigen 19-9 (CA 19–9) is currently the most used biomarker for the pancreatic cancer prognostic and monitoring [39]. However, Serum CA19–9 alone has a limited value in early detection of pancreatic cancer [40]. In addition to CA 19–9 measurements, the plasma thrombospondin-2 (THBS2) is found to be promising in accurately discriminating and distinguishing resectable tumors from locally advanced disease. Combined use of CA 19–9 with THBS2 was associated with a sensibility and specificity of 87% and 98%, respectively, in detecting pancreatic cancer [41]. Initially used to measure coagulopathy in trauma, the thrombelastography (TEG) was used to evaluate the coagulation changes in cancer patients, revealing an increased coagulation indices of patients with pancreatic adenocarcinoma [42].

The pancreatic cancer contained diverse genetic alterations [43].

According to associated gene expression, three subtypes of pancreatic adenocarcinoma had been recently defined, including “classical”, “quasi-mesenchymal”, and “exocrine like” which were respectively enriched with epithelial, mesenchymal, and digestive enzyme genes [44]. Based on tumor and stroma specificity, two respective tumor and stroma-specific subtypes had been identified and validated, including “basal-like”, “classical”; and “normal” and “activated” [45]. The basal-like tumors were found to be associated with worsened survival, compared to classical tumors [45]. Patients with classical tumor, who received modified FOLFIRINOX had the best progression-free survival [46].

The ongoing and further efforts focusing on the molecular basis of pancreatic cancer, should contribute to selecting optimal first-line systemic therapies [47].

6. Conclusion

Since the first report of pancreatic resection in the early 1900s, substantial progress of the surgical management including minimally invasive procedures resulted in reduced operative mortality rate, currently lower than 3%. The median overall survival of resected patients with pancreatic cancer has been substantially improved after introduction of adjuvant and neo-adjuvant therapies. Furthermore, the ongoing research focuses on the prevention, early diagnosis, better understanding of pancreatic cancer biological molecules, development of more effective systemic therapies, improvement of quality of life and surgical and oncologic outcomes. Additionally, for better achievement, the patient care with pancreatic cancer should be discussed in multidisciplinary team.

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