Chapter 16
Translational Approaches in Surgical Treatment

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Pancreatic ductal adenocarcinoma (PDAC) carries one of the poorest overall prognosis of all human malignancies. The 5-year survival in patients with PDAC, for all stages, remains as low as 6–7%. The low survival rate is attributed to several factors, of which the two most important are aggressive tumor biology and late stage at which most patients are diagnosed. Only 10–20% of patients are eligible for resection at presentation, 30–40% are unresectable/locally advanced, and 50–60% are metastatic [1].

Pancreatic cancer without distant metastasis can be divided into three categories: resectable, borderline resectable, and locally advanced. In absence of metastatic disease, the most important factor for improving survival and possibly offer cure is to achieve a margin-negative resection. Even after potential curative resection, most patients develop recurrences eventually, and 5-year survival of completely resected patients is only up to 25% [1]. The aggressive tumor biology and its inherent resistance to chemotherapy and radiotherapy contributes to early recurrence and metastasis.

Surgical Advances/Techniques

Pancreatic cancer surgery has evolved over the past few decades and remains the cornerstone of treatment of resectable and borderline resectable tumors. Advances in modern imaging give precise information on disease extension and vascular involvement that aids in surgical planning in order to achieve a margin-negative resection.

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Surgical techniques for pancreatic cancer include pancreaticoduodenectomy, distal pancreatectomy with splenectomy, and total pancreatectomy. Standard lymphadenectomy for pancreatoduodenectomy should include removal of lymph node stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b.

Involvement of superior mesenteric vein (SMV)/portal vein(PV) was previously considered as a contraindication for resection. However, curative resection along with SMV/PV with vascular reconstruction has now become a standard practice in specialized high-volume centers. To improve margin-negative resections, specially in borderline resectable tumors with proximity to vascular structures, SMA first approach (six different approaches) was proposed as a new modification of standard pancreaticoduodenectomy [2]. In a systematic review, SMA first approach was shown to be associated with better perioperative outcomes, such as blood loss, transfusion requirements, pancreatic fistula, delayed gastric emptying, and reduced local and metastatic recurrence rates [3, 4].

In case of arterial involvement, there is no good evidence at present to justify arterial resections for right-sided pancreatic tumors [5]. However, the modified Appleby procedure, which includes en bloc removal of celiac axis with or without arterial reconstruction, when used in appropriately selected patients, offers margin-negative resection with survival benefit for locally advanced pancreatic body and tail tumors and should be performed in high-volume centers [6].

Most evidence does not support advantage of more extended resections such as removal of the para-aortic lymph nodes and nerve plexus and multivisceral resections routinely [7–9]. Such extended resections are associated with compromised quality of life because of associated higher perioperative morbidity and intractable diarrhea. However, in highly selected patients, with preserved performance status and stable or nonprogressive disease on neoadjuvant treatment, such extended resections can provide survival advantage over palliative treatments [10]. Radical surgery in the presence of oligometastatic disease has also been reported to prolong survival in highly selected patients [11].

Translational Approaches in Surgery

Currently, the AJCC (American Joint Committee on Cancer) TNM staging is the only prognostic factor used in clinical practice to assess the survival of a resected PDAC and guide treatment decisions. However, this clinicopathological staging fails to consistently predict the outcomes after pancreatic resection. Due to the large genomic heterogeneity within PDAC tumors, prognostic gene expression signatures may be useful to predict outcome.

Earlier studies had shown that the most frequently altered genes in PDACs are KRAS, SMAD4, TP53, and CDKN2A/B (one oncogene and three tumor suppressor genes) [12–14]. Many genes were later found altered by using comprehensive genomic approaches including array-comparative genomic hybridization [15, 16].

Molecular Classification of PDAC

More recently, molecular classification according to gene expression and genomic alterations has been proposed [17–19]. The first such profiling of PDAC was published in 2011 based on microdissection performed on surgically resected specimens [17]. According to the results, PDAC was classified into three different subtypes (Collison's subtypes: "classical," "quasi-mesenchymal," and "exocrine-like"). These subtypes had different clinical outcomes and therapeutic responses and were also validated externally. The classical tumor subtype had a better survival, whereas the quasi-mesenchymal subtype had worst survival. Subtype classification was the only independent prognostic factor for overall survival (OS) in multivariate analysis and the chemosensitivity also varied among the subtypes. In another study, Moffitt et al. [18] separated the stromal component from the malignant epithelial component and identified different subtypes, based on the observation that PDAC is comprised of a dense peritumoral stroma. Two specific stromal subtypes, "normal" and "activated" stroma, were identified, with the latter showing the worst prognosis (median survival of 15 months vs. 24 months). The malignant component was further classified as "classical" and "basal-like" tumor-specific subtypes. Classical tumor and normal stroma subtypes correlated with best prognosis, and prognosis was worst with basal-like tumor and activated stroma subtypes. More recent transcriptional classification for PDAC by Bailey et al. [19] distinguished four tumor subtypes associated with different molecular pathways as "squamous," "pancreatic progenitor," "immunogenic," and "aberrantly differentiated endocrine exocrine (ADEX)." This classification is based on the differential expression of transcription factors and downstream targets important for lineage specification and differentiation during pancreas development and regeneration. Correlating with outcomes, the squamous subtype was an independent poor-prognostic factor.

Indeed, identifying such genetic signatures and their expression profiling is presently the most promising approach for identifying new prognostic tools and tailoring individualized treatment in PDAC, possibly independent of the AJCC staging.

Early Detection

Late stage at diagnosis is one of the most important factors for overall dismal outcomes in PDAC. Early detection at stage I or II can provide a window of opportunity when the disease can be eradicated by high-quality surgery and together with adjuvant chemotherapy and can result in cure [20]. Development of promising molecular biomarkers for early detection of PDAC is hence the need of the hour. For this purpose, blood-based molecular biomarkers, which include proteins, nucleic acids, autoantibodies, aberrantly glycosylated antigens, exosomes, circulating tumor cells, and metabolites, have been studied. The ideal, noninvasive biomarkers should be universally present in precancerous lesions (PanIN, pancreatic

intraepithelial neoplasia; IPMN, intraductal papillary mucinous neoplasm with dysplasia; carcinoma in situ) and should have a high sensitivity and specificity which is inexpensive, rapid, and practical to perform. Current clinical practice uses CA19-9, which is a carbohydrate antigen found on multiple carrier proteins [21]. However, it is not detectable in 5–10% of patients and lacks specificity as it is often elevated in biliary obstruction with or without malignancy. Hence, it is useful for monitoring response to therapy, but it is not a useful tool as an early detection biomarker. With molecular profiling of PDAC, a number of novel biomarkers have been discovered and are under evaluation. Also, with development of organoids recapitulating PDAC, new biomarker discovery is enhanced [22].

Circulating tumor cells (CTCs) could represent another source of blood-based molecular profiles. CTCs are tumor cells that are shed off from a primary tumor into the circulation and can be detected in the blood samples (liquid biopsy) [23]. Recently, CTCs have been studied as a potential biomarker for PDAC [24]. In this study, the authors evaluated CTC subtypes (triploid, tetraploid, or multiploid cells) and their total number and found that both were upregulated in the peripheral blood of PDAC patients when compared with healthy controls, serving thus as a diagnostic tool for the disease.

Although at present these biomarkers have not been able to make a great clinical impact, the progress made to date in finding biomarkers for early detection specially in high-risk individuals (e.g., family history of PDAC, recent-onset diabetes, chronic pancreatitis, etc.) provides optimism to the field.

Chronic Pancreatitis

Chronic pancreatitis (CP) represents a risk factor for pancreatic cancer and is a frequent differential diagnosis as well [25]. CP can involve the whole pancreatic gland or can result in development of an inflammatory head mass, which can become a considerable source of diagnostic confusion, as even high-quality CT/MRI scans fail to conclusively differentiate between the two. A positive endoscopic ultrasound (EUS) or image-guided biopsy confirms presence of a cancer; however, a negative report does not conclusively rule out malignancy. In order to enhance the diagnostic accuracy of PDAC in the background of CP, molecular markers on EUS-FNA samples have been evaluated in recent years. Utilities of DNA mutations such as kras [26], p53 [27], telomerase activity with a ribonucleoprotein enzyme [28], and a broad panel of microsatellite allele loss markers [29] have been shown to improve diagnostic accuracy in such situations.

Recently metabolic biomarkers have also been studied and introduced in this field. One such study evaluated nine metabolites [proline, sphingomyelin (d18:2,C17:0), phosphatidylcholine, isocitrate, sphinganine-1-phosphate, histidine, pyruvate, ceramide, sphingomyelin (d17:1,C18:0)] along with CA 19.9 in patients with CP having high risk for PDAC and were found to have a sensitivity of 89.9% and a specificity of 91.3% for detection of maliganacy [30].

Utilization of these molecular and metabolic biomarkers may reduce the diagnostic delay and early diagnosis of PDAC in CP and can result in early initiation of treatment and surgery in resectable patients leading to improved overall outcomes.

Summary

Given the potential clinical correlation of PDAC molecular subtyping and long-term survival, the emphasis now should be on defining a universally accepted PDAC molecular subtyping which can guide personalized therapy including surgery, irrespective the AJCC stage of the disease. Also, the focus should be on formulating an ideal biomarker for early detection of PDAC, at least in high-risk population and those with chronic pancreatitis, in order to offer early curative treatment resulting in overall improved outcomes.

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