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Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Dirk Uhlmann, FACS, MD, PhD, Chief Doctor, Professor, Department of Visceral, Thoracic and Vascular Surgery, Klinikum Döbeln, Döbeln 04720, Germany. dirk.uhlmann@klinikum-doebeln.de

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EDITORIAL

Hot topics in pancreatic cancer management

Damiano Caputo

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Damiano Caputo, Department of General Surgery, Fondazione Policlinico Universitario Campus Bio-Medico, Rome 00128, Italy

Damiano Caputo, General Surgery Research Unit, University Campus Bio-Medico di Roma, Rome 00128, Italy

Corresponding author: Damiano Caputo, FACS, MD, Associate Professor, Department of General Surgery, Fondazione Policlinico Universitario Campus Bio-Medico, Via Alvaro del Portillo, 200, Rome 00128, Italy. d.caputo@policlinicocampus.it

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a sneaky and lethal disease burdened by poor prognosis. PDAC is often detected too late to be successfully cured, and it has been estimated that it will be a leading cause of cancer-related deaths in the near future. During the last decade, multimodal treatments involving surgery, chemotherapy and radiotherapy have contributed to improving the prognosis of this disease; however, long-term results are still not satisfactory. Postoperative morbidity and mortality rates remain high, and systemic treatments are burdened by toxicity in both neoadjuvant and adjuvant settings. Advancements in technologies, targeted therapies, immunotherapy and PDAC microenvironment modulation strategies may represent useful potential weapons in the future. Nevertheless, in the fight against this dreadful disease, there is an urgent need for new, cheap and user-friendly tools for early detection. In this field, promising results have been found in nanotechnologies and "omics" analyses that search for new biomarkers to be used in primary and secondary prevention. However, there are many issues that need to be solved before considering these tools in daily clinical practice. This editorial reported the state of the art of pancreatic cancer management.

Key Words: Pancreatic cancer; Pancreatic ductal adenocarcinoma; Nanotechnology; Neoadjuvant therapy; Adjuvant therapy; Omics

Core Tip: The purpose of this editorial was to provide an up-to-date summary of pancreatic cancer management. The current state of multimodal therapies and the increasingly urgent need for development of tools for early diagnosis were summarized. The editorial also presented the high quality papers in the fields of basic, clinical, preventive and translational medicine that will help further investigations focused on this topic.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC), one of the biggest killers among solid tumors, is set to become the second leading cause of cancer-related deaths in the near future[1]. In recent years, a lot has been done in order to improve the prognosis of PDAC. However, multimodal treatments combining surgery, still considered the gold standard of care, with chemotherapy and radiotherapy in neoadjuvant or adjuvant settings have allowed only a little progress towards better outcomes. Therefore, according to Torphy *et al*[2], pancreatic cancer management still has a long way to go.

Because of the very aggressive biology of PDAC and its indolent behavior in the early stage, the battle against this dreadful disease will be fought on the fields of prevention and early detection and improving the molecular understanding of PDAC[2]. Nevertheless, the assessment of more effective systemic treatments and strategies to improve surgical outcomes will represent an important step forward in the management of pancreatic cancer. Furthermore, much is expected from developments in targeted therapies and modulation of tumor microenvironment to improve the efficacy of immunotherapies[3].

The purpose of this editorial was to provide an up-to-date summary on pancreatic cancer management. The current state of multimodal therapies and the increasingly urgent need for development of tools for early diagnosis were also summarized.

Early detection and advances in clinical diagnosis

Given that risk factors (*e.g.*, cigarette smoking, obesity, diabetes) and genetic predisposition contribute to the development of pancreatic cancer[4], it is clear that the control of the above-mentioned risk factors represents the first, although insufficient, step to prevent PDAC. PDAC is preceded by pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasm and mucinous cystic neoplasm, and follow-up guidelines of these conditions have been widely reported. On the other hand, subjects at higher risk for familial PDAC can be successfully screened by endoscopic ultrasound and magnetic resonance cholangiopancreatography[5]. One of the main issues to be solved is the identification of individuals who are at risk of the disease even in absence of positive familiar history[6].

Clearly, invasive and expensive diagnostic investigations cannot be applied indiscriminately on a large scale for asymptomatic adults[7]. On this basis, there is still an urgent need for tools for early diagnosis of pancreatic cancer that fulfill the criteria of reliability, reproducibility and cost control required by the World Health Organization[8].

Recent technological advances have led to the revision of the so called Affordable-Sensitive-Specific-User Friendly-Rapid-Equipment Free and Delivered criteria proposed in the early 2000s to the Real Time Connectivity-Ease of specimen collection-Affordable-Sensitive-Specific-User Friendly-Rapid-Equipment Free and Delivered criteria[9]. On this basis, it is clear that the development of new tools to be used for early detection of PDAC must consider the ease of collection of biological samples such as blood, saliva, urine, *etc.*

In this scenario, our group together with the researchers of the Department of Molecular Medicine of Sapienza University of Rome were among the first to exploit the potential of nanotechnologies to assist the early diagnosis of pancreatic cancer[10]. When nanoparticles interact with human fluids (*e.g.*, plasma), a shield of molecules, mostly proteins, cover them and form the so-called biomolecular corona or protein corona. Protein corona-based technologies proved their efficacy in distinguishing pancreatic cancer patients from controls with a high rate of sensitivity (up to 85%) and specificity (up to 100%)[11].

More recently, in an attempt to make nanoparticle-based diagnostic technology even more streamlined and reproducible, approaches based on the use of magnetic levitation of nanoparticles coated by personalized protein corona have been proposed. Magnetic levitation (MagLev) may overcome protein corona analysis limitations (*e.g.*, isolation of plasma proteins from nanoparticles), boosting reproducibility and clinical translation of these technologies[12].

In the attempt to search for new biomarkers to be used in the early detection of pancreatic cancer, other remarkable results have been provided by different "omics" technologies (*e.g.*, genomics,

epigenomics, non-coding RNA, metabolomics, liquid biopsy, *etc*). Studies in these fields identified many biomarkers that proved their utility alone or in panels with different combinations. Unfortunately, their application in daily clinical practice is still a long way off as large-scale validation studies are lacking, and these technologies require expensive and complex equipment[13].

As mutations in *KRAS*, *GNAS*, *CDKN2A*, *TP53* and *SMAD4* have been shown in different staged PDAC and precancerous lesions and due to "omics" analysis advancements, the opportunity of DNA-based molecular approaches for early PDAC detection is also gaining momentum. These approaches have the advantages of being based on the assessment of genetic mutations on easily obtainable samples (*e.g.*, blood, plasma)[14].

Treatment guidelines: Standards and challenges

Surgery: Surgical resection still represents the cornerstone of pancreatic cancer treatment. However, despite recent technological improvements and the increasing diffusion of the minimally invasive approaches, morbidity and mortality rates remain significant even in high-volume centers[15].

Neoadjuvant treatments: The growing number of studies supporting vascular resections, when indicated, together with the promising results obtained with neoadjuvant therapies have undoubtedly increased the rate of PDACs that are eligible for surgical treatment. Although vascular resection, mainly when arteries are involved, should be reserved in selected cases and performed in high-volume hospitals[16], neoadjuvant treatments are gaining consensus in both the scientific community and clinical practice.

In borderline resectable PDACs, higher rates of R0 resections and longer disease-free and overall survival rates have been reported when FOLFIRINOX-based neoadjuvant treatments are used[17]. Recently, a prospective multicenter phase 2 trial demonstrated promising results when gemcitabine plus nab-paclitaxel chemotherapy were administered before surgery[18]. Even though the data supporting the use of neoadjuvant therapies in resectable PDACs are more limited, this strategy is proposed in patients with "biological" borderline resectable tumors (*e.g.*, radiological resectable PDACs with elevated levels of Ca-199)[19].

In this field, a randomized phase 2 clinical trial showed the efficacy of perioperative regimens of gemcitabine plus nab-paclitaxel in terms of disease-free survival[20]. Nonetheless, for both resectable and borderline resectable PDACs, the Dutch Randomized Phase III PREOPANC Trial showed the efficacy of neoadjuvant treatments in terms of R0 resections and disease-free survival in the absence of significant improvement of overall survival rates[21]. The other side of the coin is that patients undergo significant surgical procedures for more advanced disease after chemotherapy and radiotherapy treatments contributing to high toxicity[22].

Reduction of complications, prevention and mitigation of the effects of postoperative pancreatic fistula, optimization of neoadjuvant therapies with careful selection of patients who will actually benefit from these treatments and identification of drugs and therapeutic regimens with a more favorable balance between efficacy and toxicity will represent a turning point in the management of pancreatic cancer[23,24].

Adjuvant treatments and metastatic disease: Adjuvant chemotherapy plays an important role in the treatment of pancreatic cancer. In 2013, results of the Conko-001 trial confirmed the usefulness of adjuvant chemotherapy in improving the disease-free survival rates of surgically removed PDAC[25].

Later, gemcitabine alone proved to offer the same oncological outcomes with lower toxicity when compared to 5-fluorouracil[26]. More recently, FOLFIRINOX-based regimens have led to significant improvement in overall survival, but because of their toxicity they can be administered to only very fit patients after surgery[27]. Based on the recent data reported by Choi *et al*[28], 5-fluoruracil regimens should be considered the optimal adjuvant treatment in patients with borderline resectable and locally advanced PDAC who already received neoadjuvant FOLFIRINOX. The PRODIGE 24/Canadian Cancer Trials Group PA6 just demonstrated that in resected PDACs, adjuvant FOLFIRINOX allows significantly longer survival when compared with gemcitabine[29].

Furthermore, there is increasing evidence in favor of the use of FOLFIRINOX for patients with unresectable metastatic disease[3]. On this basis, it is clear that advances have been made in the field of adjuvant therapy, but more investigations are needed. Improvement of oncological outcomes and significant reduction of toxicity are expected from targeted therapies and immunotherapy[30].

DISCUSSION

Torphy *et al*[2] has stated that much has been done but the way to win the battle against this cancer is still long. Early detection and novel therapeutic strategies represent the most urgent issues that need to be tackled. Hence, it is necessary to develop patient models and identify cheap, user-friendly and reproducible biomarkers that can be applied in daily clinical practice to assess the most effective treatment for each patient with PDAC.

Table 1 Most relevant topics in pancreatic ductal adenocarcinoma management with their current challenges and potential further perspectives

Topic	Challenges	Potential further perspectives
Prevention and early detection	Identification of high risk subjects	Nanotechnology
	Identification of novel biomarkers and signatures that satisfy the WHO REASSURED criteria	Omics technologies
Surgical treatment	Reduction of morbidity and mortality rates	Optimization of vascular resection in high skilled hospitals
Neoadjuvant treatments	Reduction of toxicity	Careful selection of fit patients
		Identification of therapeutic regimens with favorable balance between efficacy and toxicity
Adjuvant treatments	Improvement of oncological outcomes	Targeted therapies
	Significant reduction of toxicity	Immunotherapy
Biology and behavior	Lack of patient models of the tumor in order to improve translational medicine	Organoid *ex vivo* models

REASSURED: Real Time Connectivity-Ease of specimen collection-Affordable- Sensitive-Specific-User Friendly-Rapid-Equipment Free and Delivered; WHO: World Health Organization.

In this scenario, translational research is rapidly gaining ground; organoid *ex vivo* models of PDAC can be achieved from small biopsies and may represent a turning point for precision medicine approaches in cases of resectable, locally advanced and metastatic PDAC[31]. In other words, the time seems ripe to collect all the knowledge acquired in the preclinical field over the last few decades and to recommend models of PDAC in different stages that can be used to improve our diagnostic and therapeutic strategies[32].

CONCLUSION

In the very near future we will be increasingly called upon to fight the battle against PDAC. Improvements of surgical outcomes, careful selection of patients for neoadjuvant treatments and vascular resections and reduction of the toxicity of adjuvant therapies are unquestionably needed. However, in order to increase the odds of winning the battle against this lethal disease, the real gap to be filled is the assessment of cheap and easily reproducible strategies for the screening and early detection of PDAC. Indeed, the aim of this special issue was to collect quality studies in the fields of basic, clinical, preventive and translational medicine that will further help investigations focus on these topics (Table 1).

FOOTNOTES

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Country/Territory of origin: Italy

ORCID number: Damiano Caputo 0000-0001-7058-1945.

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