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EDITORIAL

Circulating tumor cells in pancreatic cancer: The prognostic impact in surgical patients

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Abstract

Pancreatic cancer is associated with a poor prognosis, even in the early stages, mainly due to metastatic progression. New diagnostic techniques that predict unfavorable outcomes are needed in order to improve treatment strategies. Circulating tumor cells (CTCs) are showing promising results as a predictive biomarker for various tumors. In this editorial we comment on the article by Zhang *et al*, who published the first systematic review and meta-analysis evaluating the prognostic value of CTCs as biomarkers in early-stage pancreatic cancer patients undergoing surgery. CTCs were detected in peripheral or central venous system blood, before or during surgery. Positive CTCs showed a correlation with decreased overall survival and decreased relapse-free, disease-free and progression-free survival in this meta-analysis. However, the heterogeneity was significant. The authors suggest that this result was related to the separation methods used between studies, but other differences such as the margin status or the neoadjuvant and adjuvant treatments used are also important to consider. CTCs may be a potential prognostic biomarker in pancreatic cancer patients, but it is necessary to compare and standardize the platforms used to isolate CTCs, to compare different biomarkers from liquid biopsy and to determine the impact on prognosis when therapeutic changes are made based on CTCs levels.

Key Words: Circulating tumor cells; Pancreatic cancer; Early-stage; Meta-analysis; Prognosis; Liquid biopsy

Core Tip: Circulating tumor cells (CTCs) are showing promising results in the diagnosis and monitoring of oncological patients. When detected before or during surgery in early-stage pancreatic cancer patients, a correlation with decreased overall survival, relapse-free, disease-free and progression-free survival has been demonstrated. However, there is an absence of homogeneity between the isolation platforms used that makes it necessary to compare them in order to introduce CTCs detection into clinical practice of pancreatic cancer.

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INTRODUCTION

Pancreatic cancer is an aggressive disease with a poor prognosis, estimated by the World Health Organization to be the seventh cancer-related cause of death in both sexes worldwide[1]. The absence of specific symptoms in the initial stages makes early diagnosis difficult with half of patients having distant metastasis at presentation. Localized disease includes resectable pancreatic cancer, borderline resectable (involves major vascular structures but remains localized) and locally advanced (unresectable but without distant metastasis). Among these patients, only 10%-15% are surgical candidates at the time of diagnosis[2]. Moreover, in surgical candidates, a high number of patients experience relapses after resection, frequently as metastatic progression[3].

Computed tomography of the chest, abdomen and pelvis and abdominal magnetic resonance imaging are the main imaging tests for the diagnosis of pancreatic cancer. Endoscopic ultrasound (EUS) also plays an important role in selected cases as it provides information on venous involvement and allows confirmation of malignancy by EUS-guided fine-needle aspiration[4]. However, diagnostic advances based on a deeper comprehension of the molecular biology of pancreatic cancer are needed to enhance early detection and treatment strategies, and identify poor prognosis factors in order to modify or intensify treatments in selected patients.

Liquid biopsy is a minimally invasive technique that allows clinicians to isolate tumor-derived circulating biomarkers from blood or other fluid samples[5]. Traditionally, carbohydrate antigen (CA) 19-9, carcinoembryonic antigen (CEA) and CA125 have been used in pancreatic cancer, but their sensitivity and specificity may be insufficient for diagnostic purposes. Recently, new biomarkers are emerging, such as cell-free DNA, circulating tumor DNA (ctDNA), tumor-specific RNA or circulating tumor cells (CTCs). CTCs are a small amount of cancer cells which originate in the primary tumor or metastasis that spread to the circulatory system. Although the majority of these cells die during the first 1 to 2.5 h, a small fraction survives and plays a significant role in the development of metastasis[6].

The incorporation of CTCs in the diagnostic process can provide various advantages. Clinical studies have shown that CTCs are an independent predictor of progression-free survival (PFS) and overall survival (OS) in different tumors, including pancreatic cancer, but not only due to their presence. Analyzing the molecular characteristics of the CTCs, as the expression of certain genes or receptors, may also have a prognostic role[7].

CTCS AS PROGNOSTIC FACTORS IN PANCREATIC CANCER

Zhang *et al*[8] published a novel paper: CTCs as potential prognostic biomarkers for early stage pancreatic cancer: A systematic review and meta-analysis. In this study, the authors evaluated the prognostic role of CTCs as biomarkers in patients diagnosed with pancreatic adenocarcinoma and a maximum tumor diameter of 4 cm, no more than three positive locoregional lymph nodes and no distant metastasis. Only studies where patients underwent surgery were included and CTCs had to be evaluated in blood samples during or before surgery. Eight studies, involving 355 patients met the inclusion and exclusion criteria and were included in the analysis. The authors concluded that the detection of CTCs is associated with decreased OS, disease-free survival (DFS), recurrence-free survival (RFS) and PFS. However, the degree of heterogeneity was significant (I^2 = 65%, P = 0.01) and the authors performed a subgroup analysis in order to detect the potential causes.

The method used to obtain CTCs was different between the studies. On the one hand, the researchers obtained CTCs from different blood samples. While five studies detected CTCs only in peripheral blood, two of them isolated CTCs both from portal venous blood and peripheral blood and one study detected them in portal and central venous catheter blood. Even though there is insufficient evidence in pancreatic cancer patients, it has been suggested that central venous blood samples contain significantly higher rates of CTCs than peripheral blood samples[9,10]. On the other hand, CTCs separation methods were not homogeneous either; while some studies used different detection kits based on biological features, others applied strategies for isolation based on the physical properties of CTCs. The authors conducted a subgroup analysis and heterogeneity was low when studies that used the CellSearch® system were analyzed independently, with decreased DFS, PFS and RFS. In a sensitivity analysis it was found that when the study by Xing *et al*[11] was excluded, the heterogeneity index of the other 7 studies decreased significantly and it was suggested that the separation method may be the cause.

However, other remarkable differences can be noticed between the 8 studies. The proportion of patients who underwent neoadjuvant and adjuvant treatments was variable. Preoperative chemotherapy was administered in the majority of patients in the studies by Semaan *et al*[12] and White *et al*[13], in contrast with only 32.1% patients in the study by Court *et al*[14], 15.1% in Xing *et al*[11], 12% in Cheng *et al*[15], 4% in Hugenschmidt *et al*[16], and none in Padillo-Ruiz *et al*[17] and Bissolati *et al*[18]. Neoadjuvant chemotherapy regimens were also different between the studies and radiotherapy was not considered in most of them. Globally there was a higher proportion of patients receiving postoperative treatments. However, chemotherapy regimens were different between the studies and there was little consideration of adjuvant radiotherapy, although it should be mentioned that when a subgroup analysis was performed, no deviation was found in treatment subgroups.

Margin status was reported in most of the included studies and the proportion of R0 varied between them, ranging from 78.6% in Semaan *et al*[12] to 37.8% in Hugenschmidt *et al*[16]. Three recent meta-analysis evaluated the prognostic role of margin status in pancreatic cancer, including one which specifically evaluated this in patients undergoing surgery after neoadjuvant treatment[19-21]. The three meta-analyses concluded that the absence of R0 status impacts prognosis, resulting in worse OS. Margin status was not assessed in the subgroup analysis conducted by Zhang *et al*[8] and its role in the high heterogeneity index of the study is not clear.

CTCS: FUTURE PERSPECTIVES

Implementation of liquid biopsy and, specifically, CTCs detection into clinical practice is becoming increasingly feasible and provides numerous advantages in terms of precision oncology. However, some limitations prevent its use from being a standard in the diagnosis and monitoring process of pancreatic cancer patients.

One limitation is the lack of standardization and comparison of platforms for CTCs isolation, which is crucial for their integration in clinical practice. In pancreatic cancer patients, the CellSearch® system is the only platform approved by the Food and Drug Administration for the detection of CTCs, but its method for isolation has some limitations and it has not been compared directly with the other platforms in pancreatic cancer patients.

Furthermore, CTCs are not the only biomarker studied in the context of liquid biopsy. Other biomarkers are also showing promising results in pancreatic cancer diagnosis and it is not clear which of them is more useful or which is the exact value of their combination. For instance, CA19.9 levels have been used as a biomarker in pancreatic cancer for decades as they have shown promise in predicting the stage and survival of patients with resectable pancreatic adenocarcinoma[22]. It has also been suggested that CEA and CA19.9 levels are useful for early detection of pancreatic adenocarcinoma as they can be elevated years before the diagnosis[23]. Another remarkable example is ctDNA, which consists of free DNA that originates from dead cells or tumor cells that shed DNA into the bloodstream and provides clinicians with a deeper knowledge of the genetic mutations of tumor cells[24,25]. Although ctDNA allows for the examination of genetic cancer characteristics at diagnosis and changes during treatment, CTCs provide information on viable disease and both biomarkers provide information on residual disease and the risk of recurrence[26]. Thus, prospective clinical trials are needed in order to determine if different biomarkers are potentially complementary for the diagnosis and monitoring of pancreatic cancer or if their predictive value increases when used together.

Finally, it is essential to evaluate the impact on patient outcomes when therapeutic changes are made based on the presence or absence of CTCs.

CONCLUSION

CTCs are a promising biomarker in cancer patients. In a meta-analysis, Zhang *et al*[8] demonstrated decreased DFS, RFS and PFS in early pancreatic cancer patients in which CTCs were isolated before or during surgery. These results are concordant with those in the literature for different tumors. However, with the rise of liquid biopsy, determining which biomarker is the most suitable for predicting distant metastasis and recurrence is still a challenge. As different platforms for CTCs detection are available, it is necessary to compare them in order to standardize their use. Also, clinical trials are needed to obtain higher levels of evidence. In conclusion, while CTCs hold promise for improving cancer diagnosis and monitoring, standardizing their isolation method and results interpretation are critical for incorporating this biomarker into clinical practice.

FOOTNOTES

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