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EDITORIAL

Serum Tumor Markers for Pancreatic Cancer: The Dawn of New Era?

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Pancreatic cancer accounts for only 3% of all cancers, but it is the fifth leading cause of cancer death in both Western countries [1] and Japan [2]. The prognosis of patients with this disease is extremely poor with less than 5% of patients alive 5 years after diagnosis. Of all the treatment modalities for pancreatic cancer, only resection offers the opportunity for a cure. However, at the time of diagnosis, approximately half of the patients already have metastases and approximately one third of patients are diagnosed as having locally advanced disease, whereas only a small proportion of patients are eligible for surgery. Most symptoms related to this malignancy occur only after disease advancement to an unresectable stages and the early diagnosis of pancreatic cancer remains challenging. To increase the proportion of pancreatic cancer patients with a chance of a cure, there is an urgent need to develop an effective screening system for asymptomatic individuals and to improve the diagnostic accuracy for pancreatic cancer in its early stage. Serum is the most ideal biological specimen for assessing tumor markers in clinical practice because of its availability for repeated collection and reproducible quantification. Recent advancements in technology and an increasing understanding of molecular biology have facilitated research programs into serum markers for pancreatic cancer.

One of the most important roles for serum markers is as a tool for cancer screening in asymptomatic populations. High-quality evidence to justify population-based screening are present for only a few specific malignancies like breast and colorectal cancers but pancreatic cancer has insufficient prevalence in the preclinical population and little availability of adequate modalities for screening. With an estimated prevalence of pancreatic cancer in the population of 0.015%, which is comparable to the latest incidence rate in Japan [3], even a test with sensitivity and specificity of 95% would yield 350 false-positive individuals for every true-positive patient. This example indicates that the screening test needs an almost 100% specificity for this malignancy.

Accuracy in diagnosis for patients with symptoms suspicious of pancreatic cancer is also required for tumor markers in order to distinguish malignancy from benign or non-invasive pancreatic disorders. CA 19-9, the most widely used serum marker for pancreatic cancer diagnosis, had been reported to have a sensitivity of 70-90% and a specificity of 70-98% [4, 5, 6, 7, 8]. Although imaging tests play the main role in the diagnosis of pancreatic cancer, serum markers including CA 19-9 have a considerable predictive value to assist the differential diagnosis in patients with abdominal discomfort or jaundice.

However, currently available serum markers are inadequately sensitive for detection of resectable pancreatic cancer. The Pancreatic Cancer Registry in Japan demonstrated that only 48.4% of the patients with small pancreatic cancer less than 2 cm in diameter had elevated CA 19-9 values [9]. Furthermore, CA19-9 values are considered useless in distinguish neoplasms with high invasive potential, such as mucinous cystic tumors and intraductal papillary mucinous tumors, from those with benign feature [10].

The most commonly accepted uses of serum tumor markers in clinical practice are for assessing the prognosis of, and therapeutic monitoring for pancreatic cancer patients because tumor marker in these situations are more valuable than other modalities including imaging diagnosis. Various studies have demonstrated that CA 19-9 is one of the most significant prognostic factors for both patients with resectable and those with unresectable disease [11, 12, 13, 14, 15]. Measurement of tumor markers as a prognostic factor provides valuable information to assist in the therapeutic decision making especially for surgeons, because early recurrence can be expected in patients with high preoperative levels of the markers. An elevated tumor marker value even after resection indicates the high possibility of remnant disease [16]. The postoperative increase in the value often anticipates the presentation of recurrence in imaging studies or of clinical symptoms. Although the measurement of the tumor size on CT or MR images is standard for evaluation in response to non-surgical treatments such as chemotherapy and radiotherapy, serial change in tumor markers assist the evaluation practically because of the difficulty in accurate measurement of pancreatic mass with obscure margin in most patients, and because of high incidence of the clinically occult progression associated with this disease [17].

Although CA 19-9 is the most useful serum marker for pancreatic cancer, it has some weaknesses. Approximately 10% of the population with the Lewis negative genotype is not able to produce CA 19-9 due to the lack of the enzyme involved in its synthesis, even if they have advanced pancreatic cancer. The Lewis gene dosage positively affects CA 19-9 value, whereas the secretor gene dosage negatively affects it [18]. Patients with small pancreatic cancer often show false negative in the CA 19-9 values. Falsely positive CA 19-9 elevation is frequently observed in patients with benign disease such as chronic pancreatitis. CA 19-9 elevation is common in patients with obstructive jaundice regardless of its malignancy and those with hapatobiliary and gastrointestinal cancer other than pancreatic cancer. Various other serum markers have been developed, although they have not displaced CA 19-9 due to its diagnostic accuracy, especially in the early stage of the disease.

Recent advances in the understanding of the molecular biology of pancreatic cancer facilitate research programs to search for novel markers including tissue-based and circulating markers. Hundreds of over-expressed genes in pancreatic cancer tissues have been identified in investigations using global gene expression. The protein product of an overexpressed gene needs several indispensable characteristics before it can become a sensitive and specific serum-based marker for pancreatic cancer: for example, it should be a secreted protein; it should be overexpressed in pancreatic cancers, it should not be expressed in the nonneoplastic pancreas, and it should have a restricted pattern of expression in other organs and tissues [19]. Several protein products of overexpressed genes including macrophage inhibitory cytokine-1 (MIC-1), synuclein-gamma, mesothelin, and osteopontin have been investigated as potential markers for pancreatic cancer, but their efficacy as serum markers remain undetermined [20, 21, 22]. Detection of aberrantly methylated genes in serum may be a useful diagnostic strategy for pancreatic cancer. The hypermethylation of CpG islands in promoter region is frequently associated with the silencing of tumor-suppressor genes such as p16/CDKN2A, E-cadherin, and others in cancer cells [23, 24]. These abnormalities have been preliminary

reported with promise as tissue- or pancreatic juice-based markers. Hypomethylation of normally methylated genes, which was reported to be identified in serum from patients with testicular cancer, has been recognized in genes including claudin 4, lipocalin 2, 14-3-3 sigma, trefoil factor 2, S100A4, and other, from pancreatic cancer cells or tissues [25, 26, 27, 28].

Proteomics, which is the mass spectrometry-based direct analysis of unknown protein in clinical specimens including serum, has also shown promise in the identification of new biomarkers. Among several technologies for proteomics researches, surface-enhanced laser desorption/ionization (SELDI)-mass spectrometry is considered to be the most useful tools available for the analysis of serum and plasma. A recent study has demonstrated a set of four mass peaks in plasma as most accurately discriminating pancreatic cancer patients from healthy controls in a training cohort with a sensitivity of 97.2% and a specificity of 94.4% and in the validation cohort with a sensitivity of 90.9% and a specificity of 91.1% [29]. The introduction of this technology has enlarged the possibility of identifying novel markers with the potential to overtake and replace CA 19-9.

A bewildering number of investigations to identify useful tumor markers for pancreatic cancer have been conducted, whereas in the vast majority of research studies over the past two decades, CA19-9 alone has been applied as the 'gold standard'. The recent accumulation of knowledge in the molecular biology of pancreatic cancer and rapid advances in technology in this field has enhanced the promising confirmation of novel serum markers with a diagnostic accuracy higher than CA 19-9. The most important obligations for these markers are higher sensitivity to detect early-stage pancreatic cancer and an almost perfect specificity in the screening for this malignancy. The enthusiasm to develop effective molecular targeted agents and other cytotoxic drugs for pancreatic cancer has been increasing rapidly after the introduction of gemcitabine and the recent FDA's approval of erlotinib. These circumstances are also highlighting the need to find the markers in serum and other biological specimens which are able to predict the response to and toxicity of the treatments.

Keywords Biological Markers; CA-19-9 Antigen; Pancreatic Neoplasms

Abbreviations MIC-1: macrophage inhibitory cytokine-1; SELDI: surface-enhanced laser desorption/ionization

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