Endoscopic ultrasound pin-points the precision medicine for pancreatic cancer

Ping Zhu, Siyu Sun
Endoscopic Center, Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China

Precision medicine (PM), also known as personalized medicine, has long been considered as the best customized treatment plan for patients. Its main purpose is to achieve the maximized therapeutic effect and the minimized side effects. More specifically speaking, it is not only closely based on personal genome information, but also combined with the relevant environmental information within proteome, metabolomics, etc. Compared to the traditional medical care, PM is considered much more targeted. In the process of conducting PM, the most important step is to adopt the latest genetic testing technology. After detecting the patient's genome, the accurate defects of the disease are directly found so as to enable the doctors to choose the PM. Therefore, this kind of medical model, with the rapid development of molecular biological techniques, is now providing us with many more opportunities to the challenges of early diagnosis and treatment of these diseases, of which the most significant one is cancer. Pancreatic cancer (PC) is a form of cancer with a high mortality rate; there are two main reasons that we know account for this: First, the patients with PC could not be diagnosed before an advanced stage due to the lack of symptoms in the early stage; second, it is due to the poor prognosis after surgical operations, radiotherapy, and chemotherapy. Recently, there has been some research which shows that we can identify mutations by making genome sequencing of the tumor tissue samples from the patients. In this way, these mutations will be an important part for early diagnosis and targeting of drugs for the precise treatment of patients.[1]

According to the K-RAS mutation analysis of PC, 95% cases of PC will have activated mutations. However, the mutations of oncogene (chronic pancreatitis, pancreatic cysts, and K-RAS oncogene in pancreatic tissue) did not occur. Therefore, this has become a reliable means of molecular biology in a PC diagnosis and differential diagnosis.[2-4] It is believed that the sample of molecular diagnosis of PC can be acquired from surgical biopsy specimens, endoscopic ultrasound (EUS)-guided fine needle aspiration (EUS-FNA) or circulating tumor cells (CTCs). When it comes to EUS-FNA, it can be justified without doubt that it has its own unique advantages.[5] This is chiefly because that the detection rate by EUS is as high as 100% for the PC whose diameter is less than 3 cm. Moreover, EUS-FNA can avoid blood vessels by using a colorful Doppler image, it has a short puncture tract and it is

Access this article online

Quick Response Code:

Website: www.eusjournal.com

DOI: 10.4103/2303-9027.175874

How to cite this article: Zhu P, Sun S. Endoscopic ultrasound pin-points the precision medicine for pancreatic cancer. Endosc Ultrasound 2016;5:1-3.

Address for correspondence
Dr. Sun Siyu, Endoscopic Center, Shengjing Hospital of China Medical University, No. 36 Sanhao Street, Shenyang - 110004, Liaoning Province, China. E-mail: sunsy@sj-hospital.org
Received: 2015-12-17; **Accepted:** 2016-01-07

easy for it to enter the small pancreatic lesions, also it can directly and accurately obtain fresh pancreatic samples between cells and tissue fluid. The samples obtained by EUS-FNA can be used to determine and identify the mutations, improve molecular diagnostic sensitivity, and also diagnose the PC that is less than 1 cm.[6,7] A recent study has shown that 60 specimens from EUS-FNA were analyzed for KRAS exon 2 and exon 3 mutations. During the process, it mainly used the following three different techniques: First, Sanger sequencing; second, the allele specific locked nucleic acid PCR; third, next generation sequencing. In general, it showed a clinical sensitivity for almost 42.1% of the KRAS mutation detection. According to the existing data, the second one accounted for 52.8% and the third one represented approximately 73.7% of the total. The results of the research claimed that next generation sequencing could improve the accuracy of KRAS mutation analysis.[8,9] Combined with 2-generation sequencing, EUS-FNA has greatly improved the diagnosis rate of the PC. However, despite the fact that EUS-FNA has combined with KRAS mutation analysis, the diagnosis rate of early PC still does not reach 100%. This is the driving force behind why many scientists are trying to improve the rate of diagnosis by other means, such as microRNA expression analysis, methylation analysis, mRNA expression analysis, and low density array Taqman analysis.[10-12] In this situation, several studies have shown clearly the clinical and molecular advantages of EUS-FNA. In addition to the combination with genomics, EUS-FNA combined with the proteomics and metabolomics are also helpful to increase the diagnostic efficiency of the early stage of the PC. After having taken both the objective and subjective factors into consideration, it is easy to conclude that the expression profiling can be regarded as a useful method in identifying biomarkers and potential target genes.[13] As to the diagnosis of pancreatic adenocarcinomas, the molecular analysis of EUS-guided FNA samples seems to be an indispensable strategy.

Besides KRAS mutations, there are also a number of factors that are closely related to PC such as various proteins among the S100 protein family. In fact, S100 protein can also be combined with RAGE, p53 gene, p21 gene, and so forth. It plays an important role in the degradation, metastasis and construction of the cytoplasmic matrix, the cytoskeleton and plasma membrane. However, the S100A2, S100A4, and S100P in S100 family have a close relationship associated with drug resistance, differentiation, metastasis, and prognosis.[14,15] Biankin[16] reported that S100A2 negative pancreatectomy patients could benefit a lot from pancreatic surgery. Although several prognostic biomarkers, such as S100A2 and S100A4, would predict the outcome of PC, however, these biomarkers can only be examined in resected specimens. But, EUS-FNA can provide a way for us to get specimens before operation to assess the level of these biomarkers. Even through several prognostic biomarkers, such as S100A2 and S100A4,would predict the outcome of PC,but these biomarkers can only be examined in resected specimens. However, EUS-FNA can provide a way for us to get specimens before operation to assess the level of these biomarkers. In a study, 123 cases were treated with EUS-FNA using a 22G Pro Core needle; the obtained specimens can work with the detection of S100A2 and S100A4. The results showed that biomarker assessment from the biopsy specimens had a great possibility to be feasible and successful. It accounted for more than 90% of the total. What's more, the presence of S100A2 and S100A4 explains both the survival and response of the patients with PC. In fact, these findings clearly demonstrate the "proof-of-concept," and also demonstrate that preoperative EUS is important to the process of clinical decision-making.[17] A case in point is the treatment selection of PC. The advocates who are performing EUS-FNA are based on the highest pretest of operable cancer. They firmly believe that it plays a critical role in establishing a definitive diagnosis. Also some others hold the view that it can preclude surgery under certain situations.[18-20]

Since the surge in biological databases, such as genomics, proteomics, metabolomics, cell analysis, and bioinformatics techniques, EUS-FNA shows its great advantages in collecting specimens in the molecular diagnosis. Generally speaking, the model of PM is developing toward the direction of the individualization and precision, and this has offered new hope for the PC patients. There is no hiding the fact that EUS-FNA can be regarded as a very promising technological partner in evaluating PC. This kind of approach has the following characteristics, such as its small invasive ability and its frugal use of resources. Also, it can provide samples for genetic and immunohistochemical detection, gene sequencing, and other test methods. It is predicted that EUS-FNA will provide a practical and efficient tool for pinpointing the precision medicine.

REFERENCES

1. Sahin IH, Iacobuzio-Donahue CA, O'Reilly EM. Molecular signature of pancreatic adenocarcinoma: An insight from genotype to phenotype and challenges for targeted therapy. *Expert Opin Ther Targets* 2015;1-19.
2. Marengo E, Robotti E. Biomarkers for pancreatic cancer: Recent achievements in proteomics and genomics through classical and multivariate statistical methods. *World J Gastroenterol* 2014;20:13325-42.
3. Zhu YP, Li QJ, Gao J, *et al*. Significance of quantitatively detecting K-ras codon 12 and 13 mutations in the tissues of pancreatic cancer and related pancreatic diseases. *Chin J Pancreatol* 2012;12:246-9.
4. Zhang MJ, Liu J, Wang S. Expression of human telomerase in pancreatic cancer: A meta-analysis. *Chinese J Gastroenterol Hepatol* 2013;22:1099-101.
5. Barresi L, Tarantino I, Traina M, *et al*. Endoscopic ultrasound-guided fine needle aspiration and biopsy using a 22-gauge needle with side fenestration in pancreatic cystic lesions. *Dig Liver Dis* 2014;46:45-50.
6. Qureshi A, Hassan U, Loya A, *et al*. Diagnostic utility of endoscopic ultrasound guided aspiration cytology in evaluation of pancreatic masses. *J Coll Physicians Surg Pak* 2013;23:484-6.
7. Suzuki R, Lee JH, Krishna SG, *et al*. Repeat endoscopic ultrasound-guided fine needle aspiration for solid pancreatic lesions at a tertiary referral center will alter the initial inconclusive result. *J Gastrointestin Liver Dis* 2013;22:183-7.
8. de Biase D, Visani M, Baccarini P, *et al*. Next generation sequencing improves the accuracy of KRAS mutation analysis in endoscopic ultrasound fine needle aspiration pancreatic lesions. *PLoS One* 2014;9:e87651.
9. Reicher S, Boyar FZ, Albitar M, *et al*. Fluorescence *in situ* hybridization and K-ras analyses improve diagnostic yield of endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic masses. *Pancreas* 2011;40:1057-62.
10. Rader AE, Avery A, Wait CL, *et al*. Fine-needle aspiration biopsy diagnosis of gastrointestinal stromal tumors using morphology, immunocytochemistry, and mutational analysis of c-kit. *Cancer* 2001;93:269-75.
11. Gleeson FC, Kipp BR, Voss JS, *et al*. Endoscopic ultrasound fine-needle aspiration cytology mutation profiling using targeted next-generation sequencing: Personalized care for rectal cancer. *Am J Clin Pathol* 2015;143:879-88.
12. Bournet B, Pointreau A, Delpu Y, *et al*. Molecular endoscopic ultrasound for diagnosis of pancreatic cancer. *Cancers (Basel)* 2011;3:872-82.
13. Mishra G. DNA analysis of cells obtained from endoscopic ultrasound-fine needle aspiration in pancreatic adenocarcinoma: Fool's Gold, Pandora's Box, or Holy Grail? *Am J Gastroenterol* 2006;101:2501-3.
14. Tsukamoto N, Egawa S, Akada M, *et al*. The expression of S100A4 in human pancreatic cancer is associated with invasion. *Pancreas* 2013;42:1027-33.
15. Ji YF, Huang H, Jiang F, *et al*. S100 family signaling network and related proteins in pancreatic cancer (Review). *Int J Mol Med* 2014;33:769-76.
16. Biankin AV, Kench JG, Colvin EK, *et al*.; NSW Pancreatic Cancer Network. Expression of S100A2 calcium-binding protein predicts response to pancreatectomy for pancreatic cancer. *Gastroenterology* 2009;137:558-68.e1-11.
17. Nguyen NQ, Ruszkiewicz A, Chang D, *et al*. Biomarker assessment from EUS guided biopsy predicts survival outcomes and surgical treatment in pancreatic carcinoma. *Gastroenterology* 2014;146:S275.
18. Yamao K, Mizuno N, Takagi T, *et al*. How I do it and when I use (and do not use) EUS-FNA. *Gastrointest Endosc* 2009;69(Suppl):S134-7.
19. Cosgrove ND, Yan L, Siddiqui A. Preoperative endoscopic ultrasound-guided fine needle aspiration for diagnosis of pancreatic cancer in potentially resectable patients: Is this safe? *Endosc Ultrasound* 2015;4:81-4.
20. Chang KJ, Nguyen P, Erickson RA, *et al*. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreatic carcinoma. *Gastrointest Endosc* 1997;45:387-93.