



Evaluating the application of next generation sequencing techniques in endoscopic retrograde cholangiopancreatography (ERCP) to improve diagnostic accuracy in patients with malignant biliary strictures

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Malignant biliary obstruction is a sinister condition that require radical treatment in order to provide the hope of a cure. Apart from complex surgery, the major clinical challenge remains the difficulty in making a conclusive diagnosis (1). There is a long list of differential diagnosis for obstruction of the bile duct including benign condition like primary sclerosing cholangitis, iatrogenic injury, infection and IgG 4 related conditions to malignant condition like carcinoma involving the whole course of bile duct, pancreatic carcinoma and adenocarcinoma in the periampullary regions (2-5).

In order to make a correct diagnosis, a very vigilant investigation from presenting history evaluation, physical examination, blood test, imaging and histological evaluation are needed. It requires a multidisciplinary team to perform all the task and to make the correct diagnosis.

One of the major pitfalls of current evaluation is that making a diagnosis depends heavily on biochemical testing (e.g., serum CEA and CA19-9 level), imaging patterns in ERCP and pathological evaluation by tissue obtained by ERCP. Unfortunately, the sensitivity of detection of cancer cell from ERCP brushing and biopsy has not been very sensitive in malignant condition ranging from lowest 8% to 67% as reported by various studies (6-10). The issue is even more complex in those scenarios where conditions maybe premalignant or radiologically malignant but the

histopathology or cytology results turn out to be benign.

An easy to perform and yet accuracy test is needed in order to diagnose this condition.

Singhi *et al.* from the University of Pittsburgh had incorporated the use of next-generation sequencing (NGS) for gene testing to endoscopic retrograde cholangiopancreatography (ERCP) to enhance the diagnostic accuracy of biliary stricture condition (11). This was a prospectively designed study to take biopsy by ERCP and using the tissue obtained to be tested against a 28 gene panel. The result showed that the sensitivity and specificity of NGS for malignant strictures was 73% and 100%, respectively. This reflects an overall improvement in diagnosis when using conventional method by evaluating CA19-9 and tissue diagnosis with pathological examination. The conventional way for making a diagnosis gave a sensitivities of 76% and 48%, and specificities of 69% and 99%, respectively. The sensitivities of diagnosis will be increased from 83% to 99% when NGS was combined with histological examination.

The use of NSG was useful in patients with other benign condition like, primary sclerosing cholangitis (PSC). The sensitivity increased from 8% when using pathological evaluation to 83% when using NGS. Alteration in genomic could be identified by this new method and cholangiocarcinoma with specific gene characteristic can

be detected. Target specific treatment could be given accordingly.

This study concluded that among the use of NGS together with conventional tissue diagnosis of biliary stricture increased the detection rate of malignant pathology. Among patients with primary sclerosing cholangitis, NGS was superior to serum CA19-9 and pathological evaluation in detecting at least high grade dysplasia.

The use of NGS for gene analysis had been shown to be useful and accurate option in other hepatobiliary and pancreatic condition. The same Pittsburgh group had performed another study for pancreatic cystic lesion, using clinical data of 626 pancreatic cystic fluid (PCF) specimens. Endoscopic ultrasound guided fine needle aspiration were performed in 595 patients. The specimen was sent for NGS Molecular analysis. The results were correlated with ancillary studies, EUS findings and follow-up (12).

Each pancreatic cystic pathology, the yield of diagnostic produced a different pattern. In Pancreatic cyst, *KRAS/GNAS* mutations were identified in 308 (49%) while alterations in *TP53/PIK3CA/PTEN* were present in 35 (6%) cases.

In patients with IPMN and MCNS, the *KRAS/GNAS* mutations detection rate were 100% and 30% respectively. The sensitivity for mucinous pancreatic cyst was 89% and 100% respectively. In comparison, *KRAS/GNAS* mutations by Sanger sequencing had a 65% sensitivity and 100% specificity.

In patients with advanced neoplasm, the sensitivity and specificity of combining *KRAS/GNAS* mutations and alterations in *TP53/PIK3CA/PTEN* was 89% sensitivity and 100% specificity by NGS.

Ductal dilatation, a mural nodule and malignant cytopathology had lower sensitivities (42%, 32% and 32%, respectively) and specificities (74%, 94% and 98%, respectively).

NGS of pancreatic cystic fluid analysis before operation for *KRAS/GNAS* mutations is highly sensitive for IPMNs and specific for mucinous PCs. The use of *TP53/PIK3CA/PTEN* alterations is a useful detection method for advanced pancreatic cancer before operation.

NGS had been proven to be an effective method in enhancing the accuracy in identifying a malignant condition in genetic level. Only a small quantity of sample was needed to provide a high sensitivity and specificity test result. This quality is extremely helpful in management of biliary stricture where only a small amount of tissue sample can be obtained.

Besides ERCP, the use of 18FDG PET CT scan may be useful to aid the diagnosis of malignant biliary stricture. Wang *et al* in a study of 66 patients demonstrated the role of PET scan preoperative evaluation (13). The maximum standardized uptake values (SUV) for malignant and benign lesions causing biliary obstruction were 8.2 ± 4.4 and 4.0 ± 5.0 , respectively ($P<0.05$). This provided a good evidence of improving specificity, sensitivity and accuracy in evaluating benign stricture from malignant tumours. The sensitivity was 86.4%, the specificity was 73.7% and overall accuracy was 83.5% when 18F-FDG PET was used.

The conventional imaging produced a sensitivity, specificity and overall accuracy of 75.8%, 68.4% and 74.1% respectively. When 18F-FDG PET/CT is combined with conventional imaging, the sensitivity, specificity and overall accuracy changed to 95.5%, 57.9% and 87.1% respectively.

The use of PET CT together with NGS gene analysis may potentially increase the accuracy of detection of malignancy in patients with biliary strictures.

To conclude, this paper written by Singhi *et al.* is one of the largest series on the application of NGS to enhance the detection rate of malignancy in patients with biliary stricture. Apart from making a correct diagnosis, the additional information of genetic analysis provided patients with tailored made subsequent treatments that will potentially prolong the survival when precision medicine could be applied.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/hbsn.2019.11.18>). The author has no conflicts of interest to declare.

Ethical Statement: The author are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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