State of the art lecture: Lithiasis and pancreatitis

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Bile duct stones

Endoscopic retrograde cholangio-pancreaticography (ERCP) has long been used as the best diagnostic method for common bile duct stones (CBDS). Moreover, it was possible to combine stone removal with endoscopic sphincterotomy (ES) during the same endoscopic session. Nevertheless it remains an invasive method, associated with complications in 5 % of patients, and with a mortality rate of 0.1–0.2 % [1, 2] for ERCP, reaching 2.2 % for ES [3 – 5]. As transabdominal ultrasound (US) or computed tomography are not particularly sensitive for the diagnosis of choledocholithiasis [6 – 7] an accurate diagnostic minimally invasive tool was awaited, to replace ERCP and to reserve ES for patients with CBDS.

In the past decade, helical computed tomodensitometry (hCT), endoscopic ultrasonography (EUS), and magnetic resonance cholangiopancreatography (MRCP) have improved the diagnosis of CBDS. More recently intraductal ultrasound (IDUS) has also been tested. Nevertheless ERCP is needed for this procedure and only ES should be avoided in patients without CBDS. Currently, what is the respective place of these modalities?

MRCP and hCT are non-invasive procedure. hCT is generally considered as inferior than MRCP, with a sensitivity of 85–88 %, specificity of 88–97 %, and diagnostic accuracy of 86–94 % [8,9], for CBDS. Nevertheless in the first comparative study [10] the results were the same with an accuracy of 86 %, a sensitivity of 88 % and a specificity of 75 % for the two procedures. The main drawback of these two techniques is the limited spatial resolution. In the first series, stones not diagnosed by MRCP were always smaller than 10 mm [11 – 13]. Imaging improvements permit now the detection of calculi smaller than 5 mm [14] but the sensitivity remains low (67 %) for stones < 5 mm as for MRCP than for hCT [10]. Moreover, MRCP is contraindicated in patients with a permanent pacemaker or metallic clips, and claustrophobic patients cannot undergo the examination, when hCT is not applicable to patients allergic to contrast medium.

EUS offers higher resolution than MRCP or hCT (0.1 versus 1 mm). The accuracy of EUS is excellent with sensitivity, specificity and accuracy ranging from 81 to 98 %, 93 to 100 % and 93 to 99 % respectively [15 – 23]. It is a minimally invasive method [20,24] with a lower failure rate than ERCP[16]. The specificity of EUS in ruling out the presence of CBDS is very high, until 98 % [25]. De-

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tection of bile duct sludge as well as minilithiasis, often missed by the other imaging techniques [26], is possible with EUS. The type of echoendoscope seems of no importance. Results are as good with radial echoendoscopes as with linear scopes [21] or with extraductal catheter probe EUS [27].

The accuracy of IDUS for the diagnosis of CBDS is also very high, reaching 100% [28–29]. The size of the probe (2 mm) allows an insertion inside the bile duct during an ERCP. The high frequency (20MHz) provides higher resolution than conventional EUS. Moon et al in 2005 compared the sensitivity of IDUS and MRCP to the results of ERCP + ES and stone removal [28]. For the detection of CBDS the sensitivity of IDUS and ERCP was 95% and 80% respectively. The clinical utility of IDUS was evaluated by Catanzaro et al [29]. The performance was compared with results of ERCP. IDUS found CBDS in 8 out of 21 patients with normal cholangiogram. ES confirmed the diagnosis in 7 patients. IDUS also avoided unnecessary ES as no lithiasis was found in 36% of patients with a positive finding on ERCP. The main drawback of IDUS remains the morbidity of ERCP which must be performed at the same time.

Very good comparative studies between these procedures are rare. In fact, to compare the performance of each technique, some parameters have to be considered. Spontaneous stone migration between the two examinations can lead to false-positive results. Stone migration has been found to have occurred in 21% of patients within 1 month [30]. Ideally, the 'gold standard' examination should be performed as soon as possible (at least during the following 2 days) after the evaluated technique. Second, ERCP (or peroperative cholangiography) is not the best 'gold standard' as its sensitivity to diagnose CBDS is around 90% [18]. Two different approaches should be considered as the most sensitive and specific : – systematic ERCP, ES and instrumental exploration of the CBD (with a Dormia basket or balloon) [18]; – depending of the result of the diagnostic tool : association of ERCP, ES, and bile duct exploration when a stone is evidenced or 6 months clinical follow-up when a stone has been excluded [20,22,23,31]. More recently the excellent results of ERCP with IDUS [10] should also lead to a third 'gold standard'.

In the first comparative studies, EUS was found to be superior to MRCP [10,32,33] or hCT [9,10,19] to detect CBDS. Improvements in imaging modalities may modify these findings: in the most recent series, the specificity of EUS and MRCP were found to be equal (97%) when sensitivity was slightly greater with EUS than with MRCP (94% versus 88%, respectively) [14]. These good results need to be confirmed in largest series. At present, EUS can be considered to be more accurate than hCT or MRCP, especially for smaller stones.

A considerable reduction in the number of inappropriate ERCP is obtained with the use of alternative imaging procedures [22,23]. Given that the accuracy of EUS is greater than that of MRCP or hCT, at least in patients with microlithiasis [13,32,33] EUS should replace diagnostic ERCP. Whenever EUS is contraindicated (total or Billroth II gastrectomy, digestive stenosis…), MRCP or hCT might be proposed. ERCP should be used in patients already known to have CBDS (shown by US, for example) or in patients with previous ES. IDUS cannot be proposed as a first step procedure because of the ERCP morbidity. It might be reserved to patients in whom CBDS have been found at EUS or MRCP, but not at ERCP.

Is it necessary to perform a systematic minimally invasive diagnostic procedure before ERCP?

Patients suspected of having CBDS on clinical and laboratory criteria and/or US findings can be ranged into risk classes from low to high [34,35]. Less than 30% of patients classified as being at moderate risk have CBDS [20,31] whereas the proportion of high-risk patients that actually have CBDS is around 70% [18,19,31,36]. For moderate- and low-risk patients, the general consensus is to perform a first-line diagnostic (after US). Thus, EUS could be the ideal alternative, selecting only those patients with bile duct stones for ERCP/ES. In high-risk patients ERCP is generally proposed as the first-line approach [20,22,31,35,37]. Nevertheless, as it is impossible completely to avoid unnecessary ERCP investigations on clinical or biochemical criteria, some authors support EUS as a first-line approach [23,38,39]. In the recent series of Liu et al [38] 140 patients presenting acute pancreatitis suspected to be of biliary origin were prospectively randomized. In the first group, EUS was followed by ERCP when needed, and in the second group, ERCP was performed immediately. EUS had a higher successful examination rate and a higher sensitivity in the detection of cholelithiasis. The morbidity was higher in the ERCP group (14% of complications) than in the EUS group (7%) but it was not significant. Then the best choice, also in high risk patients, should be to perform EUS followed, during the same endoscopic procedure, with ERCP and ES when a stone is evidenced.

Regard to cost-effectiveness, first line EUS vs first line ERCP has been studied in two situations [23,40]. In the context of laparoscopic cholecystectomy [23] EUS was performed for all patients with suspected CBDS followed by ERCP and ES when stone was evidenced. The cost of this approach was compared with the cost of a strategy proposing ERCP as first step. The mean cost for patients managed by the EUS-based strategy was significantly less than the theoretical mean cost for patients undergoing ERCP approach. In the context of acute biliary pancreatitis, Romagnuolo et al. [40] constructed a modeling standard care for non severe (selective ERCP) and severe pancreatitis (ERCP with sphincterotomy and balloon sweep). EUS was dominant in severe pancreatitis whereas it was slightly more costly in non severe (but associated with fewer ERCPs and ERCP-related complications). So, even if the estimation of cost is different depending of the countries and healthcare systems, EUS as first diagnostic tool seems to be the most effective not only for clinical impact but also for economic target. Further studies are necessary to confirm that the EUS-based strategy is also cost-effectiveness in the sub-group of high risk patients.

Gallbladder stones

US is very accurate for the diagnosis of gallbladder stones, with a sensitivity and a specificity of 97% and 95%, respectively [41]. Nevertheless sensitivity is lower in some conditions: – when US is hampered by technical problems as in obese patients; – when

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stones are too small (< 2 mm) or located in difficult area to examine (cystic duct). When there is discordance between clinical presentations (biliary-type pain) and negative US findings, the use of bile crystal analysis has long been the most common approach [42]. For ten years some series have been published confirming the interest of EUS in diagnosing small CBD stones or sludge in the gallbladder. The results were excellent compared with crystal bile analysis [43,44]. EUS was at least as accurate than crystal bile analysis [43] or even better [44] with a sensitivity of 96 % and 67 % respectively (p < 0.03) when specificity was not different (86 and 91 %, respectively). EUS has also been proved effective to diagnose small gallbladder stones in case of acute pancreatitis. So gallstones were found by EUS in 14 of 18 patients with negative findings on US by Liu et al. [25] in 2000. These results were confirmed in a larger series [26]. EUS identified unnoticed gallbladder lithiasis (sludge or very small stones) in 40 % of 168 patients referred with a diagnosis of idiopathic pancreatitis. This underlines the importance of EUS for the diagnosis of gallbladder lithiasis.

Acute pancreatitis

In patient with acute pancreatitis of unknown origin after usual explorations (history, US, biochemical tests …) EUS is mandatory [25,26,45,46]. It can help to diagnose biliary pancreatitis (see above), to evidence rare causes as small tumors or intraductal pancreatic mucinous tumors (IPMT) [26] or to suggest an underlying early chronic pancreatitis (CP). Overall, EUS should be able to find a cause for the 'idiopathic' acute pancreatitis in 80 % of patients [26]. The delay needed between EUS and acute pancreatitis is difficult to assess: when the main question concerns a possible CBDS, EUS should be done quickly to avoid unnecessary diagnosis ERCP (see above). When the question is to find an origin not evidenced by conventional tests, inflammatory parenchyma modifications should preclude to evidence a small tumor or IPMT and to conclude to an early CP. Sludge should also be overestimated in fasting patients. The most effective is probably to perform EUS 2 to 4 weeks after the attack in recovering and normally eating patients. When modifications of the parenchyma remain, the differential diagnosis between inflammatory consequences of the acute pancreatitis or modifications due to an underlying early CP can be difficult. In some cases a new EUS performed 3 to 6 months later should be useful to conclude. There is no interest to wait for recurrent attacks of acute pancreatitis to perform EUS: Yusoff et al compared the results of EUS in patients having a single episode of acute pancreatitis versus patients with recurrent pancreatitis[47]. EUS findings were not more frequent for patients with recurrent pancreatitis than for the former. The most common findings was CP which was found twice as frequent in patients with recurrent episodes vs. a single episode of "idiopathic" pancreatitis.

Chronic pancreatitis

The main question for CP is to diagnose an early symptomatic disease. This is especially important in case of acute pancreatitis or chronic epigastric pain of unknown origin (no abnormalities on conventional diagnostic methods, such as US, CT, MRI, and on non invasive pancreatic function tests). In such situations diagnosis of CP remains a difficult challenge because of different considerations:
– no 'gold standard' test is available.

No morphologic neither functional test is a perfect diagnostic test. Some of them are more sensitive when others are more specific. When comparing EUS to another test the results must be interpreted depending of the characteristics of the 'gold standard' test chosen. The risk is to create false positive results if it is highly sensitive or false negative if it is highly specific.
– CP is a progressive disease

It should be necessary, to avoid false positive diagnosis secondary to an unsatisfactory sensitivity of the test chosen as 'gold standard' to re-evaluate the diagnosis of CP some years later. Such series would certainly be the most powerful. But they are rare as more difficult to conduct.
– no specific criteria

Ideally EUS should detect subtle changes appearing early during the disease and different from the possible variations of a normal pancreas. The modifications noticed in the pancreas in case of CP can reach the parenchyma or the ducts. Wiersema et al [48] defined some criteria which can be seen. The usual scoring system includes parenchyma changes (hyperechoic foci > 3 mm, hyperechoic strands, and lobularity) and ductal changes (hyperechoic main pancreatic duct wall, dilatation of the main pancreatic duct, irregular contour of main pancreatic duct, visible side branches, cysts or calcifications). Nevertheless none of these criteria is entirely specific. Moreover, if some signs are probably more specific than others (calcification vs hyperechoic main pancreatic duct wall…) it has not been evaluated.
– necessity of a threshold

As no sign is specific the diagnosis is depending of an addition of positive items. Nevertheless, in this situation, the diagnostic threshold will completely modify the sensitivity and the specificity of the test. If the threshold is low, the test should over-diagnose the disease (false-positive results). If it is high, the test should under-diagnose it (false-negative results). Usually the presence of 1 or 2 signs is considered as non specific, 3 to 4 is equivocal, at least 5 signs is considered as probable.
– EUS criteria are operator-dependent

The inter- and intraobserver agreement of a diagnostic test is an important outcome especially for the diagnostic of subtle changes of an early disease. Wallace et al [49] tested the scoring system in a group of experienced echoendoscopists (more than 1100 lifetime pancreatic EUS examinations). The overall interobservor agreement of final diagnosis of CP was 0.45 (moderate agreement). Agreement was good (kappa > 0.50) only for 2 items: duct dilatation and lobularity. Near-consensus agreement (> 90 %) was reached in 46 % of individual EUS features. Even if these results are comparable to other commonly used endoscopic procedures such as bleeding ulcer stigmata, these results must incite any physician to be cautious when making a definite diagnosis of early CP. Computer quantitative analysis of endosonographic echogenicity of the parenchyma may provide more objective information for the diagnosis. It should overcome inter-

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observer variability in analyzing individual echo features supporting the diagnosis of CP as shown by Irisawa et al [50]. Further studies are nevertheless needed to confirm initial good results.

– population dependent

The interpretation of the results is depending of the population studied. Generally a normal pancreas presents a homogenous and slightly hyperechoic echopattern when the main pancreatic duct is thin and regular. In fact some modifications should be noticed in non pathologic pancreas, with a special correlation with age, as the pancreas may become atrophic, heterogeneous, with a pancreatic duct slightly dilated. The value of threshold figure of three or more criteria suggestive of CP was tested in patients without history of pancreaticobiliary diseases or alcohol consumption. One parenchymal or ductal abnormality at least was noted in 28% of the patients and 8% of the patients have three abnormalities. It increases with age especially after 60. The most common abnormality was the hyperechoic stranding (18%) followed by accentuation of the lobular pattern (11%) and irregular ductal contour (7.5%) [51]. Modifications can also be noticed in asymptomatic alcoholic consumers [52] or in patients with dyspepsia [53]. Whether these patients have some form of early asymptomatic CP or whether these changes are non pathologic remains questionable. In a series of patients with alcohol-related liver cirrhosis [54], EUS detected features of CP in 25% of patients who did not progress over a mean period of 22 months. Further and longer follow-up studies of such patients are needed to provide final answer.

Depending of the patient the threshold to conclude to an early CP should be modified : more than 5 criteria should be necessary to conclude to the disease in asymptomatic aged patients when presence of 3 criteria should be sufficient to conclude in a symptomatic young patient.

– cause-dependant?

Generally EUS modifications do not orientate to specific cause but in diffuse autoimmune pancreatitis. EUS may demonstrate a pancreatic enlargement, associated with a multifocal narrowing of the main duct with irregular wall thickening. At the opposite calcifications and pseudocysts seem exceptional [55, 56].

Considering these pitfalls what results should we consider?

The sensitivity and specificity of EUS to diagnose CP has been assessed with morphologic gold standards (US, CT, ERCP) and/or a functional test (secretin test) [48, 57 – 60]. Compared with ERCP, EUS has an overall sensitivity and specificity of 85% and 75%, respectively [48, 57 – 59]. Compared with pancreatic function testing (secretin test), EUS showed an overall sensitivity and specificity of 80% and 70%, respectively [48, 57] or less in smaller series [60]. As no true gold standard test exists it cannot be excluded that true cases of "early" pancreatitis were diagnosed by EUS but ignored by ERCP or secretin test inducing false positive classification. This is confirmed by Kahl et al [61] in a follow-up study. They investigated a selected group of patients with recurrent upper abdominal pain and a known history of chronic alcohol abuse. From the 130 patients included, 48% had documented attacks of acute pancreatitis. ERCP was indicative of CP in 71% of

cases. In 38 patients ERCP was considered as normal but EUS features of CP were present in 32 patients. During the follow-up (median 18 months), a final diagnosis of CP was finally done by a new ERCP in 22 of 32 patients (68.8%). In this population EUS was confirmed to be more sensitive than ERCP to diagnose early CP.

Should EUS fine needle aspiration (EUS-FNA) be helpful for the diagnosis of early CP?

Hollerbach et al [62] obtained EUS-FNA cytology in 27 patients with varying disease severity as determined by ERCP. Morphologic abnormalities reached a sensitivity of 97% and a specificity of 60%. The use of EUS-FNA slightly modifies the results with mainly an improvement of the negative predictive value from 75% to 100%. Specificity was comparable (67%). In a more recent study [63] true-cut biopsy (TCB) was used and results compared with EUS and ERCP. The agreement was poor between EUS and EUS-TCB and fair between ERCP and EUS-TCB. These results did not support the use of EUS-FNA in routine use.

At the opposite EUS-FNA should be of interest for the diagnosis of autoimmune pancreatitis. In the series of Farrell et al. [56], EUS guided FNA was suggestive of chronic inflammatory pancreatitis in 9 of 12 patients. As the risk of false positive FNA exists [64] the use of TCB instead of FNA may provide better diagnosis and seems safe in a short series [65].

Finally is EUS really helpful when a CP is suspected?

Probably yes to exclude the disease: when less than two criteria are present EUS can reliably allow avoiding more invasive procedure. Nevertheless further long term follow-up series are needed to confirm that EUS can really exclude the disease.

Certainly yes to confirm the disease even when other tests as ERCP are negative, but a lot of pitfalls exist and we have to remain cautious when giving this result:

– The characteristics of the patient must be considered: age, alcohol consumption, recent acute pancreatitis, chronic epigastric pain.
– The number of present items: more they are more the diagnosis is probable.
– The experience of the endosonographer.

Further studies are needed to consider the respective accuracy of each item considered in the EUS scoring system and to precise the follow-up of mild symptomatic patients with slight features suggesting of CP.

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Invited papers

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