

## DEVELOPMENTS IN DIGESTIVE ENDOSCOPY

Andrea May, Marco Bruno and Bjorn Rembacken Lectures —  
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Review by Guido N. J. Tytgat

Prof Andrea May from Germany covered endoscopic achievements in the upper gastrointestinal tract. There is no global consensus on the need and the characteristics of surveillance of patients with esophageal columnar metaplasia (Barrett). Most would agree that surveillance is only clinically indicated when the neoplastic risk is truly enhanced. Based on a large cohort of over 1,000 esophageal early adenocarcinoma, cancer was more common in long segment Barrett (> 3 cm) (56%) compared to short segment (< 3 cm) metaplasia (24%). The authors conclude that the cancer incidence per 100,000 population is 3.3 for long segment compared 1.4 for short segment. Based on these findings, it would appear that Barrett length should be integrated in the surveillance advice: every 2–3 y for long segment, every 5 y for short segment. We are again reminded that surveillance is a difficult procedure, requiring optimal equipment, optimal dedication, and expertise for adequate detection of neoplasia. In a prospective surveillance study of routine clinical practice of 121 patients with Barrett neoplasia, only one third of the neoplastic lesions were correctly identified at endoscopy. The other two thirds were initially considered as non-suspicious aberrations; particularly type IIb (flat, non-elevated) were prone to misinterpretation. Because detection and proper identification of flat neoplasia is difficult, it is probably still wise to take 4-quadrant non-targeted biopsies during the index endoscopy to diminish the risk of missing neoplastic changes.

Peroral endoscopic myotomy (POEM) was added to pneumodilation and laparoscopic Heller myotomy for the treatment of achalasia. The long-term results of the large multicenter prospective trial comparing pneumodilation to laparoscopic myotomy have become available. In that study, re-pneumodilation was allowed twice if this therapy was initially successful and if symptoms recurred beyond 2 years after the first pneumodilation; treatment failure was decided if symptoms recurred sooner. Respective per protocol 5 years success was 91 versus 82%, and intention-to-treat success was 82 versus 84% for pneumodilation and laparoscopic myotomy; perforation occurred in 5% after pneumodilation and mucosal injury occurred in 12% after myotomy. This study therefore illustrates that both techniques are comparable from a clinical point of view. The choice of therapy should at large be based on local expertise. Certainly in the younger patients (< 40 y) myotomy by an experienced surgeon deserves to be considered. While the technique of POEM continues to improve, follow-up data from the initial studies are becoming available. 80 patients from a multicenter study were followed-up for 2–3 years. The initial success rate of 96% dropped to 78% beyond 2 years of follow-up. Initial failure (4%) and disease recurrence (18%) occurred mainly during the learning phase of the procedure. Endoscopic reflux esophagitis was diagnosed in 40% (!) of the patients, usu-

ally requiring prolonged PPI therapy. POEM is certainly an attractive novel procedure but may not be superior to the other treatment modalities, and cannot yet be recommended as the new standard therapy of choice.

Endoscopic hemostasis with hemostatic powder (such as hemospray etc) continues to be explored particularly with respect to the proper indications (diffuse bleeding, difficult bleeding areas to reach, failure of other hemostatic modalities, etc. In a study with 40 patients with upper-intestinal, non-variceal bleeding, initial hemostasis was obtained with hemospray in 95% but bleeding recurred in 30%. Interestingly, no hemostatic powder was endoscopically detectable after 24 hours. For the time being, hemostatic powder should be considered as a reserve method together with the standard endoscopic hemostatic modalities: injection of saline / epinephrine; mechanical clipping and ligation; thermal electrocoagulation.

The number of patients on anticoagulants (vitamin-K antagonists, such as warfarin or the novel oral anticoagulants, such as dabigatran) that need an endoscopic procedure is increasing. Low risk procedures are upper and lower endoscopy + biopsy, biliary or pancreatic stenting, and diagnostic EUS. High risk procedures include: polypectomy, sphincterotomy, EUS with fine needle aspiration, PEG, variceal banding and stricture dilation. To prevent peri-operative bleeding, inpatients with atrial fibrillation, warfarin is usually stopped 5 days before the procedure and low-molecular weight heparin is given as peri-operative bridging. Warfarin can be resumed within 24 hours after the procedure. In a large study with almost 2,000 patients with atrial fibrillation, heparin was compared with placebo as bridging in patients with a mean CSAD2 score of 2, 3; arterial thromboembolism occurred in 0.3 versus 0.4% but major bleeding in 3.2 versus 1.3% respectively in the heparin versus the placebo group. The authors conclude that for low risk interventions and a CHAD2 score = < 2, no bridging with heparin is required and warfarin can be resumed within 2 hours after the procedure at the usual dose. Currently, the CHA2DS2-VASc scoring system is often used. Following points are given: congestive heart failure 1, hypertension 1, age =>75 y 2, diabetes 1, stroke 2, vascular disease 1, age 65–74 1, female gender 1.

Interest in full (transmural) thickness resection of localised mural lesions throughout the gastrointestinal tract is rising, and dedicated full thickness resection devices have recently been described. Obviously such technology should be in the hand of highly experienced endoscopists, in a center with full expertise in endoscopic emergencies, but the expectation is that such endoscopic approaches will expand. The wall defect is usually closed before transmural transection, with a large over-the-scope (OTC) clip. An alternative is to suture the defect with a suturing device (over-stich; plicator; Gerdx etc).

Balloon-assisted endoscopy is increasingly performed in patients with Crohn disease. In a retrospective analysis of almost 30,000 patients examined with balloon-assisted endoscopy, the overall perforation rate was 0.1%, but the risk increased 2.5 fold in Crohn, 3 fold in steroid users and 9 fold in the latter combination. Utmost attention is therefore mandatory in the presence of ulcerated lesions and concomitant steroid therapy. A rising alternative to endoscopy is dedicated MRI enterography for primary diagnosis but also for monitoring therapy. There is even some hope that in the future, MRI-based differentiation between inflammation and fibrosis will be possible and quantifiable, which will have major impact in the choice of therapy.

Prof Marco Bruno from the Netherlands covered the recent findings of clinical relevance in the biliopancreatic area with ERCP and EUS. First discussed was a landmark study regarding the role of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction. These are patients with pain after cholecystectomy without significant abnormalities on imaging or laboratory studies. Sphincterotomy was randomly compared to sham, and those randomized to sphincterotomy and had an elevated pancreatic sphincter pressure were rerandomized to biliary only, or biliary and pancreatic sphincterotomy. Over 200 patients were included. To make the story short, the results were negative! The lesson for us clinicians is that we should be utterly reluctant to embark on risky sphincterotomy for a pain syndrome which is poorly understood. Further discussed was the role of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction, which is commonly performed in the USA. In a landmark multicenter American sham-controlled randomized trial involving over 200 patients with pain after cholecystectomy, without significant abnormalities on imaging or laboratory studies and without prior sphincter treatment or pancreatitis, sphincterotomy was compared to sham therapy with follow-up blinded lasted for 1 year. After ERCP patients were randomized irrespective of sphincter manometry findings. Those randomized to sphincterotomy with elevated pancreatic sphincter pressure were randomized again to biliary or to both biliary and pancreatic sphincterotomy. The outcome was essentially negative; sphincterotomy (either biliary or combined biliary and pancreatic) was no better than sham placebo in relieving symptoms. Physicians should therefore be utterly reluctant to carry out a (risky) sphincterotomy if in the absence of imaging or lab abnormalities. Already in a somewhat older study, it was shown that rectal NSAIDs reduce the incidence of post-ERCP pancreatitis, which occurred in 9% of the indomethacine group, compared to 17% in the placebo group. Based on such findings, it is usually recommended to administer rectally 100 mg indomethacine or diclofenac before or after ERCP, especially in patients with an elevated baseline risk [suspected sphincter of Oddi dysfunction; prior pancreatitis; pre-cut sphincterotomy; > 8 cannulation attempts; sphincter dilation; ampullectomy] or in patients with 2 or more minor criteria [age > 50 y; female gender; prior recurrent pancreatitis; > 3 contrast injections in the pancreatic duct; high pressure acinarization; duct cytologic sampling]. Perhaps these recommendations for rectal NSAIDs may not be as straight forward as initially thought because of the findings in a large general practice study (with ~70% at average post-ERCP pancreatitis

risk) comparing 100 mg rectal indomethacine versus placebo suppository. The study did not show protection against pancreatitis, defined by new upper abdominal pain, lipase > 3 fold the upper normal level, and need for hospitalization. Putting all information together (including some recent positive studies), it is probably wise to still continue to use rectal NSAIDs in clinical practice. By the way, parenteral administration of NSAIDs has not been shown to be effective as pancreatic prophylaxis in the past for unknown reasons.

It is widely accepted that palliative drainage of malignant common bile duct obstruction should be first attempted endoscopically. Initial insertion of a 10 Fr plastic stent is recommended if the diagnosis of malignancy is not established or if expected survival is < 4 m. No drug prescription is recommended to prolong stent patency. In patients with an established diagnosis of malignancy, initial insertion of a 10 mm diameter self expanding metal stent is recommended if expected survival is > 4 m or whenever the cost of such a stent is less than half the ERCP cost. A recent study with over 200 patients compared stent patency for plastic stents (172 d), uncovered (288 d) and partially covered self-expanding metal stents (299 d). Total costs per patient at the end of the follow-up period did not differ between plastic stents and metal stents. Even in patients with < 3 m survival or metastatic disease, costs did not differ. Thus in the palliation of extrahepatic biliary obstruction, self expanding metal stents have a longer functional time and total costs do not differ significantly with stent type.

The standard endoscopic therapy for choledocholithiasis is endoscopic sphincterotomy and basket or balloon facilitated stone extraction. Complimentary techniques for removal of large or multiple stones are mechanical lithotripsy, electrohydraulic lithotripsy, cholangioscopy with (Holmium) laser lithotripsy or extracorporeal shockwave lithotripsy. To find out if it is possible to extract large (>15 mm) or multiple (>3) stones after widening the sphincterotomy opening with a large balloon, a comparative study was performed in 70 patients comparing sphincterotomy with or without balloon dilation. Complete stone removal was achieved overall in respectively 100 vs 89%; in the first session in 88 vs 56%; pancreatitis occurred in 6 vs 23%; hemorrhage in 3 vs 6%; there were no perforations. Papillary large balloon dilation, with or without endoscopic sphincterotomy was retrospectively analysed in 2 other studies and revealed similar rates of large / multiple stone removal (100 vs 98%) and adverse event rates (4 vs 7%). Based on these data, American guidelines state that papillary large-balloon dilation can be used as the initial method when large common bile duct stones have been identified.

If retrograde cannulation of the biliary tree fails in case of distal malignant obstruction, percutaneous transhepatic cholangiography is often attempted. The latter technique may lead to complications (bleeding, bile leak, sepsis, peritonitis) and may cause mortality (0.6–5.6%). Novel is the possibility of EUS guided transmural drainage, preferably using an all-in-one device for puncture and deployment of a partially covered metal stent or increasingly, a lumen-apposing (diabolo-type) stent. A multicenter Korean study compared EUS-guided internal versus percutaneous drainage for unresectable malignant distal biliary obstruction and inaccessible

papilla. Respective technical success was 94 vs 97%, functional success was 88 vs 87%, adverse events 9 vs 31%, reintervention rate 25 vs 55%. Stent patency and overall survival were comparable. It would appear that EUS-guided internal biliary drainage may well become the therapy of choice in the future now that stent design and equipment continues to improve.

Conflicting data have been reported regarding the clinical impact of on-site cytopathology evaluation during EUS-guided fine needle aspiration of pancreatic masses. Observational studies have suggested that the absence of on-site cytopathology is associated with a 10–15% reduction in definite diagnosis and number of adequate specimens. Because a randomized controlled trial, comparing the impact of on-site cytopathology on the diagnostic yield and overall accuracy is lacking, a large American trial was conducted involving 240 patients. Respectively with versus without on-site cytopathology revealed a median number of needle passes of 4 vs 7, inadequate specimens of 10 vs 13% and overall accuracy of 88 vs 89%. It would therefore appear that in high volume centers there is no difference in the diagnostic yield of malignancy, accuracy, procedure time and costs between patients with pancreatic masses undergoing EUS-fine needle aspiration with or without on-site cytopathology. An obvious alternative to all this would be that the endoscopist of the future obtains some basic training in cytology slide production and evaluation, but whether this is realistic remains to be seen.

Prof Bjorn Rembacken (UK) analysed endoscopy in the lower gastrointestinal tract. He first discussed the important issue of bowel cleansing. Most difficult to clean are the elderly, cirrhotics, constipated and obese patients. Adding lubiprostone to the polyethylene glycol (PEG) solution does not help. A split-dose regimen gives overall better results than the day-before cleansing, but same day cleansing is even better than splitting over 2 days. The better the cleansing result, the more sessile serrated lesions and advanced adenomas are detected, and the lesser flat lesions are missed. The higher the experience, the higher the cecal intubation rate (usually somewhat lower in women and the elderly). Cap-assisted colonoscopy has been shown to improve the adenoma / polyp detection rate, especially in the right colon. Prolonging the withdrawal / observation time beyond 6 months

increases the polyp detection rate but also decreases the risk of interval cancer occurring after the colonoscopy. Using a spasmolytic (often mebeverine) during the procedure may marginally improve the procedure. Endoscopic retroversion, not only in the rectum but also in the right colon enhances the adenoma detection rate. Water infusion in a difficult sigmoid reduces pain and improves the adenoma detection rate, but not the cecal intubation rate. The presence of a large, flat, dysplastic polyp in the left colon points to a higher risk of polypoid lesions in the proximal colon, stressing the need for standard meticulous pan-colonoscopy. Small polyps can be removed by cold-snaring or with a large caliber forceps. Larger lesions, not suitable for snare polypectomy, are increasingly removed by endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). A meta-analysis of EMR versus ESD, involving well over 2,000 polyps, showed following respective results: perforation 1.4 vs 5.7%; delayed bleeding 3.5 vs 2.0%; procedure duration 30 vs 66–108 m.

Of the several (ESGE, ACG) guidelines that were discussed only a few items will be covered: regarding bowel cleansing, avoid sodium phosphate and magnesium citrate preparations in the elderly, or patients with renal disease, or those taking medications that alter renal blood flow or electrolyte excretion. Avoid metoclopramide. Offer a repeat colonoscopy within 1 year in patients with inadequate preparation. If small bowel bleeding persists, the diagnostic work-up should include a repeated upper and lower endoscopy, capsule endoscopy, balloon-enteroscopy, CT or MR enterography as appropriate. Intra-operative endoscopy should be available at the time of surgery. Patients with aortic stenosis and angiodysplasia (Heyde syndrome) and ongoing bleeding should undergo aortic valve replacement.

The American guidelines on surveillance after colorectal cancer surgery were also covered.

- For stage I cancer and risk factors: CEA twice / y / 5 y; colonoscopy after 1 y and then every 3–5 y; 5 yearly CR or MRI
- For stage II to III cancer: CEA twice yearly for 5 y; colonoscopy after 1 y and then every 3–5 y; 5 yearly CT or MRI.
- For stage IV metastatic disease: CEA twice yearly for 5 y; colonoscopy after 1 y and then every 3–5 y; 5 yearly CT or MRI