Surgical Symposia during the 14th UEGW, Berlin, Germany, 2006

P. Berberat^a H. Friess^a H.G. Gooszen^b D.J. Gouma^c O.R.C. Busch^c J.J.B. van Lanschot^c

^aDepartment of Surgery, University of Heidelberg, Heidelberg, Germany; ^bDepartment of Surgery, University Medical Centre of Utrecht, Utrecht, and ^cDepartment of Surgery, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Pancreatic Cancer

Monday, October 23, 2006
14th UEGW, Berlin, Germany

Presenters: G. Klöppel (Kiel, Germany),
J.P. Neoptolemos (Liverpool, UK),
H. Friess (Heidelberg, Germany), C. Bassi (Verona, Italy)

Pancreatic cancer is a devastating disease which belongs to one of the top five causes of cancer deaths in the Western world. Long-term survival still remains very poor with an overall 5-year survival rate of 0.5–5%. So far resection is the only chance for cure. At the time of diagnosis, only about 10% of the patients are resectable. However, most of the patients who undergo potentially curative resection show local recurrence or distant metastasis during follow-up. Recent randomized controlled trials showed that post-operative adjuvant treatment may improve long-term survival. Furthermore, several new agents have become available which may have significant antitumour activity. Additionally, modern molecular biology and genetics revealed new insights into how this aggressive malignancy may develop and progress. The question remains of how these new findings will have an impact on the daily management of patients with pancreatic cancer in the near future. Finally, due to safer pancreatic resections in specialized centres with low mortality and morbidity rates, the question of how aggressive the resection can or should be done was revitalized in recent years.

In the well-attended pancreatic cancer symposium four opinion leaders discussed these hot and interesting topics.

Günter Klöppel gave an overview of the new insights into the pathogenesis of ductal adenocarcinoma and its genetic background. These tumours, which include infiltrating duct-like and tubular structures embedded in highly desmoplastic stroma, consistently show expression of the cytokeratins 7, 8, 18 and 19. Furthermore, they often express MUC1, a glycoprotein which is normally a marker of intralobular ductal cells. Moreover, other typical duct cell

markers are found, such as CA 19-9, DUPAN-2, SPan1, and CEA. In parallel with other tumours, it was recently discovered that also the invasive pancreatic ductal adenocarcinoma is most probably the result of a stepwise tumour progression from early dysplastic lesions to invasive carcinoma. Five years ago, a panel of specialized pathologists proposed a classification of precursor lesions of ductal adenocarcinoma [1]. The so-called PanIN classification includes four types of PanIN lesions: PanIN 1A, PanIN 1B, PanIN 2 and PanIN 3, which represent different degrees of structural dysplasia and cytological atypia finally leading to invasive ductal adenocarcinoma. Genetically, ductal adenocarcinoma shows both activation of oncogenes and inactivation of tumour suppressor genes. The well-known players were discussed which are mutated in pancreatic carcinogenesis: K-ras oncogene (80%), CDKN2A/p16 (60%), TP53/p53 (50%), SMAD4/DPC4 (50%) and telomerase activity (95%). Recently it was shown that the stepwise morphological changes in the precursor lesions are associated with these genetic alterations [2]. Several studies revealed that the rising incidence of loss of heterozygosity for p16, p53 and DPC4 is associated with an increasing PanIN grade. On the other hand mutated K-ras and telomerase activity, which are already seen in PanIN 1 lesions, represent most probably very early genetic events. Light will be shed on the time frame during which invasive ductal adenocarcinoma develops and answers will become available concerning the implications of the PanIN lesions for the patients' prognosis.

Helmut Friess discussed the impact of genomics on the management of patients with pancreatic cancer. He underlined that we still need to better understand the biology of pancreatic cancer and to find the mechanisms which make this tumour so aggressive. The clinical problems of local aggressiveness, early invasion and infiltration, early formation of distant metastasis and resistance to neoadjuvant treatment have to be solved. The molecular findings in the last 15 years were reviewed [3]. It was shown that by activation of growth factors and their receptors, the local tumour growth of pancreatic cancer is significantly stimulated. Furthermore, the deregulation of growth inhibitory mechanisms leads to a further increase of tumour growth. Moreover, other

genes were identified which seem to influence the invasive nature of pancreatic cancer such as heparanase and the urokinase plasminogen activator and its receptor. The well-known neural invasion of pancreatic cancer cells seems to be triggered by overexpression of the nerve growth factor and its receptor TrkA. Finally, through apoptotic and antiapoptotic genes, pancreatic cancer seems to develop treatment resistance. Through the new molecular biological techniques more and more of such causative genes in the pathogenesis of pancreatic cancer are discovered. Just in the last few years the increasing knowledge concerning genomics led to the first practical application in the management of pancreatic cancer patients: the frequent K-ras mutation serves as a new diagnostic tool to identify pancreatic cancer. Furthermore, the first clinical trials have been initiated to evaluate if selective targeting of these K-ras mutations (farnesyltransferase inhibitors, antisense K-ras, and K-ras peptide vaccinations) is a realistic therapeutic option. Phase II and phase III studies with inhibitors of growth factors and growth factor receptors such as VEGF and EGF receptor in combination with standard chemotherapy (gemcitabine) showed promising early results with prolonged survival.

It was concluded that numerous molecular alterations have been identified in pancreatic cancer and that with new pharmaceutical developments, several of these alterations might be successfully targeted [4]. However, their benefit concerning the survival of pancreatic cancer patients is still to be proven in clinical trials.

John Neoptolemos provided an overview of the latest development in the adjuvant therapy of pancreatic cancer. The recent randomized controlled trial from the European Study Group for Pancreatic Cancer (ESPAC 1) showed a significant survival benefit for adjuvant chemotherapy, whereas no survival benefit was observed for chemoradiation [5]. Including ESPAC 1, a total of five randomized controlled trials of adjuvant treatment in patients with histologically proven pancreatic ductal adenocarcinoma were reported in the last years. A recently published meta-analysis of these five trials demonstrated again a significant benefit of adjuvant chemotherapy with a 25% reduction in the risk of death [6]. The median survival was estimated at 19 months with chemotherapy and 13.5 months without. The 2-year and 5-year survival rates with chemotherapy were estimated at 38 and 19%, respectively, and 28 and 12% without. Furthermore, a subgroup analysis in this meta-analysis showed that chemoradiation might be more effective than chemotherapy in patients with positive resection margins. Therefore, further studies with novel chemoradiation techniques should be performed in patients with positive resection margins. Most of these randomized controlled trials were performed with 5-fluorouracil (5FU). A recent report from Oettle et al. [7] showed that gemcitabine induces a significant prolongation of the disease-free survival in the adjuvant setting of pancreatic cancer (7.5 vs. 14.2 months). Final survival data of these trials are still pending. Furthermore, the ESPAC 3 trial, which is under way and has recruited more than 1,000 resected pancreatic cancer patients, will clarify whether there are advantages of gemcitabine in comparison to 5FU treatment. Several new agents were discussed, showing a significant antitumour activity in the palliative setting in patients with pancreatic cancer: gemcitabine plus erlotinib (EGFR inhibitor) or gemcitabine plus capecitabine (oral 5FU) have just recently been shown to moderately improve survival compared with gemcitabine treatment alone. Another phase II trial which combines gemcitabine with cetuximab (antibody against EGF receptor, EGFR) showed a me-

dian survival time of 5 months in patients with EGFR-positive tumours. A phase III trial comparing cetuximab plus gemcitabine with gemcitabine alone is ongoing. Moreover, the combination of gemcitabine and bevacizumab (antibody against VEGF) demonstrated in a phase II trial a promising median survival time of 9 months with 26% partial response and 45% stable disease over 5 months. Also with this drug a phase III trial in a randomized controlled setting is under way. Furthermore, all these drugs, which show significant but still small effects on survival in the palliative treatment, will need to be tested in the adjuvant setting. Over the last few years much scientific attention has been paid to the development of new therapeutic strategies in patients with pancreatic cancer, as indicated by a steady increase of the number of abstracts presented at the major cancer meetings. In the coming years it will become clear how effective the many drugs truly are which are already on the market or are currently being developed.

In the last presentation Claudio Bassi reported on the role of portal vein replacement in pancreatic cancer surgery. Pancreatic tumours often involve the portal and/or superior mesenteric vein. Under these circumstances R0 resections are only possible with en bloc resection of the involved vessel. The question remains whether or not such an extensive procedure benefits the patients. The recently published systematic review was discussed concerning the outcome of the synchronous portal/superior mesenteric vein resection during pancreatectomy for cancer [8]. The authors compiled over 1,600 patients of 52 different studies. They demonstrated a mortality rate of 6% (range: 0–33%) and a morbidity rate of 42% (range: 9–78%). Histological evidence of venous invasion was present in 64%, while 40% of the patients revealed an R1 resection and 67% showed positive lymph nodes. The median survival time was 13 months with 1-, 3- and 5-year survival rates of 50, 16 and 7%, respectively. The authors pointed out that based on the high rate of lymph node metastasis and the low 5-year survival rate, it is unlikely to cure patients with radical resection when the tumour invades the portal vein. The study was especially criticized for its heterogeneity and the application of non-standardized surgical techniques. It was underlined that in high-volume centres the outcome after pancreatectomy with portal vein resection is comparable to that without vein resection. This supports the conclusion of Fuhrman et al. [9] from 1996: 'Venous involvement is a function of tumour location rather than an indication of aggressive tumour biology.' By showing his own data from Verona, Professor Bassi demonstrated that the survival for patients with portal vein resection is not as good as for patients with R0 resection without portal vein involvement. This is most probably due to the fact that also in his experience it is difficult to reach an R0 resection as soon as the portal vein is involved. One should be aware of the fact that pancreatic cancer is often a systemic disease and that extended surgery alone is not enough to cure the patient. Therefore, in order to achieve better results the focus has to be put on the development of efficient adjuvant therapeutic strategies.

In summary, this session gave an interesting and updated overview concerning the latest developments in basic research, surgical techniques and adjuvant therapy for pancreatic cancer. A better understanding of the pathogenesis of this cancer and the molecular biology of its development and progression, the development of new techniques in radical surgery and finally the availability of many new drugs and targets for adjuvant treatment leave hope for major progress in the near future.

References

- 1 Hruban RH, Adsay NV, Albores-Saavedra J, Compton C, Garrett ES, Goodman SN, Kern SE, Klimstra DS, Kloppel G, Longnecker DS, Luttges J, Offerhaus GJ: Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. *Am J Surg Pathol* 2001;25:579–586.
- 2 Hruban RH, Wilentz RE, Kern SE: Genetic progression in the pancreatic ducts. *Am J Pathol* 2000;156:1821–1825.
- 3 Shi X, Friess H, Kleeff J, Ozawa F, Buchler MW: Pancreatic cancer: factors regulating tumor development, maintenance and metastasis. *Pancreatol* 2001;1:517–524.
- 4 Kleeff J, Michalski C, Friess H, Buchler MW: Pancreatic cancer: from bench to 5-year survival. *Pancreas* 2006;33:111–118.
- 5 Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pedrazzoli P, Pap A, Spooner D, Kerr DJ, Buchler MW; European Study Group for Pancreatic Cancer: A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004;350:1200–1210.
- 6 Stocken DD, Buchler MW, Dervenis C, Bassi C, Jeekel H, Klinkenbühl JH, Bakkevoel KE, Takada T, Amano H, Neoptolemos JP; Pancreatic Cancer Meta-Analysis Group: Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. *Br J Cancer* 2005;92:1372–1381.
- 7 Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutherlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H: Adjuvant chemotherapy with gemcitabine vs. observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007;297:267–277.
- 8 Siriwardana HP, Siriwardana AK: Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatic resection for cancer. *Br J Surg* 2006;93:662–673.
- 9 Fuhrman GM, Leach SD, Staley CA, Cusack JC, Charnsangavej C, Cleary KR, El-Naggar AK, Fenoglio CJ, Lee JE, Evans DB: Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. *Ann Surg* 1996;223:154–162.

Acute Pancreatitis

Monday, October 23, 2006
14th UEGW, Berlin, Germany

Presenters: J.-L. Frossard (Geneva, Switzerland),
O. Le Moine (Bruxelles, Belgium),
H.G. Gooszen (Utrecht, The Netherlands),
M. Raraty (Liverpool, UK)

Jean-Louis Frossard covered the pathophysiology of systemic inflammatory response syndrome (SIRS). SIRS is a systemic inflammatory response to any insult of any kind of injury. The reaction of the patient to the insult depends on the severity of the insult and the reaction to the insult. The reaction, called compensatory anti-inflammatory response syndrome, is largely determined by pre-existing co-morbidity like malnutrition, renal failure or diabetes. The more intensive and effective the initial pro-inflammatory response is, the lower the anti-inflammatory response and the quicker the immunological status returns to the normal equilibrium. In the pathogenesis of SIRS, several mediators – e.g. chemokines, toll-like receptor, macrophage inflammatory factor

and TNF- α – play a role and most of them are aspecific as for their role in acute pancreatitis.

Acute pancreatitis should be considered as a multistep disease process with an initiation, an amplification and a complication phase, with a pancreatic injury and blood toxicity phase starting within the first 2–4 h, followed by a lung injury phase starting within 12 h. The exact role of chemokines, toll-like receptor, MIF, MIP and TNF- α with their counteracting mechanisms has to be further unravelled to open up strategies for specific treatment.

Olivier Le Moine summarized the role of early endoscopic retrograde cholangiopancreatography (ERCP). Since the first trial by Neoptolemos et al. [1], there has been confusion about who needs ERCP plus endoscopic papillotomy (EPT) in case of acute pancreatitis and when this should be performed.

There is increasing awareness that the group of patients with idiopathic pancreatitis is smaller than originally thought and that a proportion of these patients, probably even 50%, should be classified as gallstone patients even though gallstones cannot be detected on abdominal ultrasound, endoscopic ultrasound or MRI. This potentially enlarges the group of patients that are candidates for ERCP/EPT in case of acute pancreatitis.

A meta-analysis on the role of sphincterotomy has shown an absolute risk reduction of over 10% for morbidity and around 5% for mortality.

The recent study published by Acosta et al. [2] focusing on the duration of obstruction has clearly demonstrated that ERCP/EPT within 48 h after onset of the disease improves prognosis in terms of morbidity, complications and hospital stay, but not in terms of mortality.

None of the current randomized controlled trials (RCTs) has targeted the therapeutic window (within 48 h of the onset of symptoms).

It has never been shown that endoscopic sphincterotomy should be performed only in the presence of a visible stone at ERCP. The role of microlithiasis and oedema is unclear.

Hein Gooszen discussed the pros and cons of enteral nutrition and probiotics. There are four strategies to prevent infection of necrosis in patients with acute pancreatitis: prophylactic use of antibiotics, selective bowel decontamination, enteral nutrition and the use of probiotics.

The use of enteral nutrition, early in the course of acute pancreatitis, irrespective of the suspected course of the disease, has become common practice after 8 RCTs. Although the trials are all relatively small and not uniform in design and although strategies that were compared were not comparable, the overall outcome was quite uniform. It has been shown that enteral feeding is to be preferred over parenteral feeding because the incidence of infections and complications as well as the mortality rate decrease. Besides all these advantages, enteral feeding is cheaper than parenteral feeding. The working mechanism is not known but there is evidence suggesting that the commensal flora is favourably supported.

Probiotics, used with or without enriched enteral feeding (prebiotics), have been tested in RCTs with patients undergoing abdominal surgery including liver transplantation. In three studies the number of infectious complications was significantly lower in the group that received pre- and probiotics. The effectiveness of pre- and probiotics in acute pancreatitis has not been clearly demonstrated yet and the results of a multicenter Dutch randomized trial have to be awaited to allow a more definite conclusion. Experimental studies in rats with acute pancreatitis indicate that probiotics lower the number of intraluminal pathogens in the small

bowel, are capable to decrease bacterial translocation and improve survival if the probiotics are used in a strict prophylactic setup.

Michael Raraty discussed the role of surgery. The concepts of surgical treatment of acute pancreatitis have changed considerably over the last decade and the mortality of necrotizing pancreatitis has dropped from 40–60 to 20%. The role of surgery is to prevent the second peak of mortality, in the 3rd to 4th week after onset of disease and caused by secondary infection of the pancreatic and peripancreatic necrosis.

Complete and early necrosectomy by an extensive laparotomy is, at least in Liverpool, gradually being replaced by less invasive techniques to reduce morbidity and to make surgery amenable to more – sicker and older – patients.

This is largely based on an increasing referral practice and a dedicated group to develop this less invasive technique. The groups from Glasgow and Liverpool have developed the technique of step-by-step removal of retroperitoneal necrosis through a sinus tract, i.e. preferably through the left flank in the window between left colon and kidney. Although morbidity has decreased considerably, mortality is still around 20%.

Treatment of acute pancreatitis is not completed after the necrosis has been successfully removed and the patient has recovered. Elective cholecystectomy as the final step must be scheduled. The recurrence rate for acute pancreatitis is 35% and justifies removal of the gallbladder as soon as possible after the attack of pancreatitis has subsided. Whether this also holds true for patients who have undergone successful papillotomy early in the course of the disease is unknown. Theoretically, the risk for recurrence may be less, but there are no data in the literature to support this. Although not supported by solid data, most experts believe that in cases of mild pancreatitis cholecystectomy should be performed during the same hospital admission and that for the more severe cases, cholecystectomy should be scheduled 'as soon as technically feasible', i.e. after recovery from the severe attack.

References

- 1 Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP: Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. *Lancet* 1988;2:979–983
- 2 Acosta JM, Katkhouda N, Debian KA, Groshen SG, Tsao-Wei DD, Berne TV: Early ductal decompression versus conservative management for gallstone pancreatitis with ampullary obstruction: a prospective randomized clinical trial. *Ann Surg* 2006;243:33–40.

Developments in the Management of Common Bile Duct Stones

Tuesday, October 24, 2006
14th UEGW, Berlin, Germany

Presenters: M. Delhay (Bruxelles, Belgium),
H. Neuhaus (Düsseldorf, Germany),
A. Paganini (Rome, Italy),
J.S. Laméris (Amsterdam, The Netherlands)

This symposium was an excellent update on the diagnostic workup and treatment of bile duct stones.

Myriam Delhay started with an overview of the optimal diagnostic strategy. The clinical and biochemical diagnosis is not very accurate, i.e. neither very specific nor very sensitive (55 and 76%, respectively). For the selection of subsequent radiological tests it might be helpful to differentiate between high probability (>50%), intermediate probability (50–20%) and low probability (<20%) for the presence of common bile duct (CBD) stones, in order to identify patients for endoscopic retrograde cholangiopancreatography (ERCP; probably first group) or magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) [1]. An overview of 5 prospective studies comparing MRCP and EUS showed no difference in performance, a positive predictive value of 0.87 versus 0.93%, respectively, and a negative predictive value of 0.92 versus 0.96%, respectively. There was high agreement between both procedures [2]. For patients with biliary pancreatitis a decision analysis model was evaluated by Arguedas et al. [3]: ERCP versus MRCP followed by ERCP versus EUS followed by ERCP versus observation with intraoperative cholangiography. It was concluded that MRCP has potential advantages over EUS in grading the severity of pancreatitis, but that EUS might be better to identify small stones particularly in the major papilla area.

It was concluded that one should probably prefer MRCP or EUS prior to ERCP in patients with a low/intermediate probability of CBD stones. There is no difference in the performance of both procedures and the choice is dependent on the availability of each technique and on the local skills and costs. If both techniques are available, MRCP should probably be the first test and, if negative in patients with high clinical suspicion, it should be followed by EUS.

Horst Neuhaus summarized the endoscopic approach for the treatment of CBD stones. The recent Cochrane systematic review of Martin et al. [4] reported a higher ductal clearance by surgery in the era of open cholecystectomy, but no difference in clearance of endoscopic treatment versus laparoscopic surgical treatment. The use of ERCP, however, necessitates increased numbers of procedures per patient.

Identical results are reported in a recent meta-analysis [5]. Overall success rate of ductal clearance by endoscopic or surgical treatment was 77 versus 80%, respectively, and mortality was 1.7 versus 0.9%, respectively [5]. Both approaches have a similar outcome and the choice between the two should be based on local expertise. Currently, endoscopic sphincterotomy (ES) is generally the first choice in most European countries.

Data from 3 randomized controlled trials comparing the endoscopic and surgical approach were summarized, showing no difference between both procedures in terms of clearance of the duct and recurrence.

Concerning the management of the gallbladder after ES, a recent trial from Hongkong showed that the gallbladder should be removed, because of a relatively high incidence of recurrent biliary complaints in patients with a gallbladder in situ [6].

The discussion of stents after ERCP (in patients with unsuccessful stone removal) is still ongoing. This procedure will eventually lead to a high incidence of cholangitis (63%) and stone removal by alternative techniques is advocated, including extracorporeal shock wave lithotripsy (ESWL) or transpapillary laser.

Alessandro Paganini discussed the 'single stage' (laparoscopic) surgical approach. In a consecutive series of 344 patients he found that the procedure could be completed in 96%. A trans cystic approach was used in 58% and the other 42% of patients was managed by a laparoscopic transverse choledochotomy [7, 8]. There

were only 8 major complications (3%) and 1 patient died. Remarkably, during long-term follow-up none of the patients had recurrent attacks of cholangitis, recurrent ductal stones or strictures [8]. This might be due to the transverse incision of the duct. It was concluded that laparoscopic CBD exploration is an effective, safe, single stage management of gallstones and CBD stones.

Finally, Han Laméris discussed the role of interventional radiology in gallstone disease. Percutaneous intervention should be considered if endoscopy fails, if cannulation fails (diverticulum) or if endoscopy is considered to be too invasive (dyspnoeic patients). Access to the biliary system is generally obtained via the transhepatic or the transcystic route or via the T tube tract after surgery.

Stone removal is performed after fragmentation by mechanical lithotripsy, ESWL or laser therapy and finally flushing the bile duct. In a series of 100 patients reported by Garcia-Vila et al. [9], the success rate was 95%. Nearly half of the patients were treated by a percutaneous transhepatic approach and 46 via the T tube tract. Five patients suffered from severe complications (especially haemobilia in 4 of these patients). Another possibility after successful percutaneous transhepatic cholangiography (PTC) is the so-called 'rendezvous' procedure in which PTC is combined with the endoscopic approach.

It was concluded that the percutaneous approach is a highly successful (90%) alternative if endoscopy fails.

The overall conclusion from this symposium might be that the diagnostic workup nowadays is non-invasive by using MRCP and/or EUS. ERCP is only acceptable in patients with a very high suspicion of the presence of CBD stones.

Primary treatment is endoscopic removal by ES followed by laparoscopic cholecystectomy for fit patients or a 'single-stage' laparoscopic stone removal from the CBD in combination with cholecystectomy. The radiological approach is a highly successful alternative for failures of standard treatment.

References

- 1 Ainsworth AP, Rafaelsen SR, Wamberg PA, Durup J, Pless TK, Mortensen MB: Is there a difference in diagnostic accuracy and clinical impact between endoscopic ultrasonography and magnetic resonance cholangiopancreatography? *Endoscopy* 2003;35:1029–1032.
- 2 Verma D, Kapadia A, Eisen GM, Adler DG: EUS vs. MRCP for detection of choledocholithiasis. *Gastrointest Endosc* 2006;64:248–254.
- 3 Arguedas MR, Dupont AW, Wilcox CM: Where do ERCP, endoscopic ultrasound, magnetic resonance cholangiopancreatography, and intraoperative cholangiography fit in the management of acute biliary pancreatitis? A decision analysis model. *Am J Gastroenterol* 2001;96:2892–2899.
- 4 Martin DJ, Vernon DR, Toouli J: Surgical versus endoscopic treatment of bile duct stones. *Cochrane Database Syst Rev* 2006;2:CD003327.
- 5 Clayton ESJ, Connor S, Alexakis N, Leandros E: Meta-analysis of endoscopy and surgery versus surgery alone for common bile duct stones with the gallbladder in situ. *Br J Surg* 2006;93:1185–1191.
- 6 Lau JY, Leow CK, Fung TM, Suen BY, Yu LM, Lai PB, et al: Cholecystectomy or gallbladder in situ after endoscopic sphincterotomy and bile duct stone removal in Chinese patients. *Gastroenterology* 2006;130:96–103.
- 7 Paganini AM, Guerrieri M, Sarnari J, De Sanctis A, D'Ambrosio G, Lezoche G, Lezoche E: Long-term results after laparoscopic transverse choledochotomy for common bile duct stones. *Surg Endosc* 2005;19:705–709.
- 8 Paganini AM, Guerrieri M, Sarnari J, De Sanctis A, D'Ambrosio G, Lezoche G, Perretta S, Lezoche E: Thirteen years' experience with laparoscopic transcystic common bile duct exploration for stones: effectiveness and long-term results. *Surg Endosc* 2007;21:34–40.
- 9 Garcia-Vila JH, Redondo-Ibanez M, Diaz-Ramon C: Balloon sphincteroplasty and transpapillary elimination of bile duct stones: 10 years' experience. *Am J Roentgenol* 2004;182:1451–1458.

Iatrogenic Perforations

Tuesday, October 24, 2006
14th UEGW, Berlin, Germany

Presenters: P. Malfertheiner (Magdeburg, Germany),
R. Schoefl (Linz, Austria), S. Jackson (Plymouth, UK),
O.R.C. Busch (Amsterdam, The Netherlands)

This symposium focused on the diagnosis and management of iatrogenic perforations due to endoscopy. Although the incidence of iatrogenic perforation is low, it seems to rise due to an increase in diagnostic endoscopies and especially therapeutic endoscopies. All the presenters stressed the necessity of an individualized approach for the diagnosis and treatment of this complication by a multidisciplinary team. Such a team should include a gastroenterologist, a radiologist and a surgeon. These specialties were all presented at this symposium.

Peter Malfertheiner gave an overview of the various sites and organs which can be perforated by endoscopic means [1, 2]. He clearly showed that therapeutic interventions had a much higher incidence of perforation than diagnostic procedures. In the oesophagus, stomach and duodenum endoscopic mucosectomy and sphincterotomy during endoscopic retrograde cholangiopancreatography (ERCP) were responsible for most of the perforations whereas in the colon diagnostic colonoscopy also caused perforations. In his own centre a perforation rate of 0.11% was found in almost 28,000 procedures. During therapeutic endoscopies perforations occurred in 0.44% as compared to 0.014% during diagnostic procedures. Of these perforations 55% needed surgical intervention while the rest could be treated conservatively. Only 1 patient died (mortality 0.003%). For adequate treatment early detection is mandatory and doctors should avoid denial if there is even the least suspicion of perforation. Conservative management is only a treatment option in selected cases without signs of peritonitis or sepsis. Medical treatment consists of supportive care, antibiotics and antisecretory agents and is dependent on the localization, timing and condition of the patient.

In the second presentation Rainer Schoefl discussed the possibilities of endoscopic treatment of perforations. For the oesophagus it is clear that surgery is demanding and conservative management is a good alternative. Covered stents can be used to seal off a persistent leak in order to prevent intrapleural contamination. Because only small uncontrolled studies report advantages of these stents, evidence for their additional value over conservative treatment is lacking. It seems important to place these stents in an early phase in order to prevent mediastinitis. Four weeks after successful placement the stent should be removed.

Gastric perforations mainly occur after endoscopic resection (ER) of early mucosal lesions and can be treated by clipping of the gastric wall. The largest series is from Japan by Minami et al. [3] who treated 121 gastric perforations (4.9% of 2,460 patients) after ER. In this centre of excellence endoscopic clipping was successful

in 98.3% giving the same recovery rate as in the non-perforated cases.

Perforations after ERCP and sphincterotomy occur in 0.3–0.6% and could be treated conservatively in most cases. In older series early surgery had a mortality rate of up to 30%. To ensure biliary drainage to the gut most endoscopists insert a temporary plastic endoprosthesis. Close observation is mandatory to recognize failures in an early state because these patients should be treated surgically. Sometimes an abscess develops in the retroperitoneum which needs drainage.

Colorectal perforations occur after diagnostic procedures but more frequently after polypectomy. Heldwein et al. [4] showed an incidence of 9.7% complications of which 90% were minor and could be treated conservatively; the incidence of perforation was 1.1% and polyp size and location were risk factors for this complication. Risk factors for perforation were polyp size and location in the right colon. Just as for upper gastrointestinal lesions, colorectal perforations are frequently repaired endoscopically by clipping although evidence for the effectiveness of this treatment is lacking. If peritonitis develops, surgery is needed, which is preferably performed laparoscopically to minimize surgical trauma.

Simon Jackson gave an overview of the diagnostic modalities and stressed that early diagnosis is important and improves outcomes. Plain radiography can display free air in only 50–70% of cases and for oesophageal perforations contrast imaging has false-negative results in 10–38%. Therefore, cross-sectional images (especially CT scans) are used in these cases more frequently. CT can show free air, but especially in postoperative patients this sign is non-specific. Extravasation of contrast on CT has an almost 100% specificity; moreover, additional diagnostic signs can be identified on CT, such as bowel wall thickening, enhancement or discontinuity, mesenteric infiltrates and free retro- or intraperitoneal fluid collections. Sensitivity of CT to confirm perforation was only 86%; therefore, it is advised after negative imaging to perform close clinical observation and perhaps even interval imaging. Interventional radiology plays an important role in the treatment of abdominal complications. The success rate of percutaneous drainage of intra-abdominal abscesses is over 90%.

In the last presentation regarding the surgical treatment of iatrogenic perforations Olivier Busch stressed that timing of intervention is important and surgery should not be reserved only as last resort. Immediate surgical consultation is mandatory to obtain an adequate multidisciplinary management. If the underlying disease has not yet been treated, surgical resection might be the best option and should be performed before advanced inflammation appears. Prompt operation for oesophageal perforation enables primary closure of the defect or resection with direct reconstruction. Several studies have shown that postponed operations have a higher mortality and morbidity rate. For intra-abdominal perforations, such as in the stomach and colon, surgery could be performed laparoscopically. Clear indications for surgery are the presence of (generalized) peritonitis and an untreated underlying disease. Also when duodenal perforation following ERCP leads to retroperitoneal abscess formation, surgical intervention is required. This is preferably done by minimally invasive techniques, making surgery less traumatic. In conclusion, all authors agreed that iatrogenic perforation needs a multidisciplinary management to achieve the best individualized approach.

References

- 1 Huber-Lang M, Henne-Bruns D, Schmitz B, Wuerl P: Esophageal perforation: principles of diagnosis and surgical management. *Surg Today* 2006;36:332–340.
- 2 Putcha RV, Burdick JS: Management of iatrogenic perforation. *Gastroenterol Clin North Am* 2003;32:1289–1309.
- 3 Minami S, Gotoda T, Ono H, Oda I, Hamanaka H: Complete endoscopic closure of gastric perforation induced by endoscopic resection of early gastric cancer using endoclips can prevent surgery. *Gastrointest Endosc* 2006;63:596–601.
- 4 Heldwein W, Dollhopf M, Rosch T, et al: The Munich Polypectomy Study (MUPS): prospective analysis of complications and risk factors in 4000 colonic snare polypectomies. *Endoscopy* 2005;37:1116–1122.

Management of Acute Upper Gastrointestinal Bleeding

Wednesday, October 25, 2006
14th UEGW, Berlin, Germany

Presenters: R. de Franchis (Milano, Italy),
I. Racz (Gyor, Hungary),
J.J.B. van Lanschot (Amsterdam, The Netherlands),
J.S. Laméris (replacing O.M. van Delden;
Amsterdam, The Netherlands)

Roberto de Franchis addressed the question whether oesophageal varices need medical treatment or endoscopy. Over the last decades, in-hospital mortality of variceal bleeding has decreased from 50 to 20% and expert centres have even reported percentages below 15%. Early rebleeding in cirrhotic patients occurs mainly within 5 days. Vasoactive drugs have been proven effective. Based on randomized controlled trials (RCTs) it is advised to start these drugs (somatostatin, octreotide, etc.) as soon as possible (i.e. even prior to endoscopy) and to maintain these drugs for 2–5 days. Cirrhotic patients have an increased risk of infection and this risk is further increased by bleeding, partly because haemorrhagic shock enhances bacterial translocation. Rebleeding and mortality are significantly higher in patients with an infection than in those without an infection. Antibiotic prophylaxis decreases infection rate with 32% and mortality rate with 9% in cirrhotic bleeding [1]. Endoscopic treatment of acute variceal bleeding has been proven highly effective in several RCTs. Rubber band ligation is the recommended form of endoscopic therapy, although sclerotherapy may be used in the acute setting if ligation is technically difficult [2]. These endoscopic treatments are best used in association with pharmacological therapy, which preferably should be started prior to endoscopy. Recent data suggest that it is useful to correct coagulation defects with recombinant activated factor VII as an adjunct to endoscopic plus vasoactive treatment [3]. Finally it might be effective to place self-expanding covered metal stents when first-line endoscopic and pharmacological treatment has failed. These stents should be removed 2–14 days later [4].

Istran Racz discussed the role of endoscopy. Roughly half of the acute upper gastrointestinal bleedings are caused by gastroduodenal ulcers. Immediately following acute haemorrhage, the majority (60%) of ulcers have a clean base, while only 10% show active bleeding. Early endoscopy in the emergency room imme-

diately after admission does not seem to have any advantages over a procedure in the endoscopy unit within 24 h, although this conclusion is based on a relatively small sample size. If, during emergency endoscopy, the source of bleeding cannot be identified, rebleeding and mortality increase 6-fold. The combination of injection therapy plus bipolar coagulation is more effective than each modality on its own [5]. Endoscopic clipping is equivalent to the combination of injection and coagulation [6]. If at emergency endoscopy an adherent clot is identified, one is placed for a therapeutic dilemma to remove the clot (with the potential risk of inducing a rebleed) in order to allow proper injection therapy or not to remove the clot and thus to rely upon proton pump inhibition. The most recent trial does not show relevant advantages of one approach over the other [7].

Jan van Lanschot discussed under which circumstances surgery is indicated in case of a bleeding peptic ulcer. The conventional strategy for massive ulcer bleeding consisted of resuscitation, endoscopic localization of the bleeding site and surgical therapy, ranging from intraluminal and extraluminal vessel ligation to local (gastric) ulcer excision and formal gastric resection. Three major developments have dramatically changed this field. Potent medical acid suppression (first H₂-receptor agonists and later proton pump inhibitors) is crucial, because blood coagulation and platelet aggregation are most effective in a pH-neutral environment. Moreover, several endoscopic techniques have been developed to stop an acute bleeding. Finally, definite cure can be achieved by eradication of *Helicobacter pylori* and by discontinuation of NSAIDs (if possible). Therefore, the aim of emergency surgery should be to control the bleeding securely, rather than to prevent ulcer recurrence. What is currently the optimal timing of surgery? Lau et al. [8] have shown in a randomized trial that in case of rebleeding endoscopic re-intervention reduces complications with mortality similar to surgery. Therefore, the first rebleeding is preferably treated again endoscopically, with the possible exception of a massive bleeding from a large ulcer at the posterior wall of the duodenal bulb. Only limited data are available on the optimal type of surgical therapy in case of a second rebleeding. In a large retrospective study no significant differences were identified between minimal (i.e. non-resectional) and aggressive (i.e. resectional) surgery [9]. Because of the extremely negative selection of patients (50–70% ASA class 3–4) surgical intervention is presently accompanied with a high mortality rate, although the underlying disease and the impact of surgery rather than rebleeding are the major cause of death [10, 11]. In order to minimize the negative impact of surgical trauma transcatheter embolization is a promising novel tool.

Finally, Han Lamris addressed the role of embolization. Angiography and embolization (A&E) are indicated, if the bleeding site cannot be reached endoscopically, if bleeding recurs after two endoscopic procedures or after surgery and if the patient is a poor surgical candidate. In order to visualize the bleeding at angiography, the patient should have clinical signs of bleeding or the endoscopist should see an active bleeding. In general, this equals a loss of at least 3 units of red blood cells per 24 h. Multidetector CT scanning is increasingly helpful to localize more subtle and more complicated sources of bleeding [12].

In the upper gastrointestinal tract the presence of arcades/dual vascularization decreases the risk of ischaemia, but increases the risk of persistent bleeding from other branches. Technical success of A&E is defined as successful visualization and embolization of the bleeding site; in recent series it varies between 95 and 98%. Clinical success is defined as the absence of rebleeding and is substantially lower (50–60%) [13]. Ischaemic complications are mostly feared and in general well below 10%, but other complications (including allergic reactions, renal failure and bleeding at the puncture site) should also be taken into account. As yet, no studies are available comparing A&E with other secondary interventions.

References

- 1 de Franchis R: Evolving consensus in portal hypertension. Report of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2005;43:167–176.
- 2 Lo GH, Lai KH, Cheng JS, et al: Emergency banding ligation versus sclerotherapy for the control of active bleeding from esophageal varices. *Hepatology* 1997;25:1101–1104.
- 3 Bosch J, Thabut D, Bendtsen F, et al: Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology* 2004;127:1123–1130.
- 4 Hubmann R, Bodlaj G, Czampo M, et al: The use of self-expanding metal stents to treat acute esophageal variceal bleeding. *Endoscopy* 2006;38:896–901.
- 5 Calvet X, Vergara M, Brullet E, Gisbert JP, Campo R: Addition of a second endoscopic treatment following epinephrine injection improves outcome in high-risk bleeding ulcers. *Gastroenterology* 2004;126:441–450.
- 6 Saltzman JR, Strate LL, Di Sena V, Huang C, Merrifield B, Ookuba R, Carr-Locke DL: Prospective trial of endoscopic clips versus combination therapy in upper GI bleeding (PROTECT-UGI bleeding). *Am J Gastroenterol* 2005;100:1503–1508.
- 7 Kahi CJ, Jensen DM, Sung JJ, Bleau BL, Jung HK, Eckert G, Imperiale TF: Endoscopic therapy versus medical therapy for bleeding peptic ulcer with adherent clot: a meta-analysis. *Gastroenterology* 2005;129:855–862.
- 8 Lau JY, Sung JJ, Lan YH, Chan AC, Ng EK, Lee DW, Chan FK, Suen RC, Chung SC: Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. *N Engl J Med* 1999;340:751–756.
- 9 de la Fuente SG, Khuri SF, Schiffnert T, Henderson WG, Mantyh CR, Pappas CN: Comparative analysis of vagotomy and drainage versus vagotomy and resection procedures for bleeding peptic ulcer disease: results of 907 patients from the Department of Veterans Affairs National Surgical Quality Improvement Program Database. *J Am Coll Surg* 2006;202:78–86.
- 10 van Lanschot JJB, van Leerdam M, van Delden OM, Fockens P: Management of bleeding gastroduodenal ulcers. *Dig Surg* 2002;19:99–104.
- 11 Sarosi GA, Jaiswal KR, Nwariaku FE, Asolati M, Fleming JB, Anthony T: Surgical therapy of peptic ulcers in the 21st century: more common than you think. *Am J Surg* 2005;190:775–779.
- 12 Yoon W, Jeong YY, Shui SS, Liu HS, Song SG, Jang NG, Kim JK, Kang HK: Acute massive gastrointestinal bleeding: detection and localization with arterial phase multi-detector row helical CT. *Radiology* 2006;239:160–167.
- 13 Schenker MP, Duszak R, Soulen MC, Smith KP, Baum RA, et al: Upper gastrointestinal hemorrhage and transcatheter embolotherapy: clinical and technical factors impacting success and survival. *J Vasc Intern Radiol* 2001;12:1263–1271.