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Future perspectives

FUTURE PERSPECTIVES

Transluminal endoscopic treatment of pancreatic fluid collections

During the last decade the technique of endoscopic drainage of pancreatic fluid collections (PFC) has rapidly developed but level A evidence is mostly lacking, probably because of its rapid ongoing development. Lack of randomized studies, heterogeneity of the included PFC's (including our randomized controlled trial described in **chapter 3**), differences in the definition of clinical success, lack of long term follow up, and retrospective nature of the majority of studies, make it difficult to extrapolate these results from literature into daily clinical practice. ^{1-7, 11-13} Only in case of uncomplicated, solitary, "true" pseudocysts (without debris) endoscopic drainage has proven to be superior to open surgery in a recent randomized controlled trial.¹⁴ Improvements in EUS-guided drainage of uncomplicated pseudocysts are still possible and questions about optimal timing, type and length of drainage and necessity of pancreatic duct imaging and therapy remain open. In chapter 3 we showed that a newly developed forward-viewing echoendoscope does not seem to be of additional value in routine clinical practice. Future (comparative) prospective studies should focus on long term outcome of endoscopic drainage of a homogenous population. Preparations are underway for an international randomized controlled trial investigating removal versus leaving transluminal stents in place after endoscopic drainage of pancreatic fluid collections complicating acute pancreatitis based on pancreatic ductal anatomy (REMOVE trial).

During the last 5 years, we (chapter 4) and other groups showed that endoscopic transluminal necrosectomy (ETN) is an effective and safe minimally invasive therapy in selected groups of patients with walled-off pancreatic necrosis (WOPN). The retrospective nature of these studies makes implementation of this therapy into daily clinical practice difficult. It seems to be important to distinguish sterile and infected WOPN. The current standard for patients with sterile WOPN is conservative. However, some patients with sterile WOPN remain symptomatic, despite several weeks or months of conservative treatment. Because of the low morbidity rate of ETN, patients with persisting symptoms of sterile WOPN may benefit from relative early endoscopic intervention (6-8 weeks after onset). Prospective studies concerning patients with symptomatic sterile WOPN are necessary to determine if and when ETN may be indicated in these patients. On the contrary, for the majority of patients with infected WOPN, intervention is indicated but the role of endoscopic drainage is not completely clear yet. Currently, these patients are treated by a minimally invasive step-up approach starting with percutaneous catheter drainage and, if necessary, followed by videoscopic-assisted retroperitoneal debridement.¹⁵ A nationwide randomized controlled trial to compare this strategy with endoscopic therapy has just been funded by different sources and received Ethics committee approval: Transluminal endoscopic versus surgical necrosectomy in patients with infected pancreatic necrosis: a randomised controlled multicentre trial (TENSION trial; ISRCTN09186711).

Natural Orifice Transluminal Endoscopic Surgery

Besides endoscopic therapy aimed at organs adjacent to the gastrointestinal tract, such as the pancreas, we and others have shown that it is technically feasible to perform intraperitoneal surgery via the natural orifices in animals. The current question is whether intraperitoneal pure NOTES procedures are ready for human randomized clinical trials. In our opinion, the answer should probably be 'not yet'. There are still fundamental challenges that need to be surmounted before pure NOTES procedures are ready for randomized clinical trials.

As described in **chapter 9, 10 and 11**, the NOTES peritoneoscopy in its current form is inferior to laparoscopic peritoneoscopy in detecting intraperitoneal metastases in animal and in human cadaver models. In all three chapters the majority of missed simulated metastases were located at the (inferior) surface of the liver. Limited visualization of the inferior liver surface is best explained by the inability to adequately lift and retract the liver lobes while maintaining an adequate overview. This lack of triangulation is mainly caused by the fixed parallel relationship between view and instrument axis. Secondly, the necessary force to retract or lift the liver lobe, cannot be exerted at the tip of a flexible endoscope as it diminishes over the course of a long and floppy endoscope and is therefore too small. Dedicated endoscopic platforms and/ or endoscopic accessories designed for transluminal instead of intraluminal use, need to be developed before the NOTES peritoneoscopy could be translated into human clinical trials. Such undertakings will require a large amount of effort to be taken on by investigators collaborating with technical universities and/ or industry.

If these challenges can be overcome, the NOTES peritoneoscopy will represent a paradigm shift in gastrointestinal cancer staging. Imagine a patient presenting with obstructive jaundice secondary to, for example, a pancreatic neoplasm. After EUS and fine needle aspiration, if findings are positive, a transluminal peritoneoscopy for staging can be immediately be performed with the patient under simultaneous sedation during the entire procedure. When peritoneal metastases are identified, an ERCP with permanent biliary drainage can be performed, again in the same setting, thus avoiding further need for workup, surgical intervention, and general anesthesia.

The earlier described limitations of the NOTES peritoneoscopy also hold true for other, more complex NOTES procedures, such as the endoscopic transluminal cholecystectomy. Although the majority of NOTES research worldwide focused on the transluminal cholecystectomy, current endoscopic technology hampers the development of a pure NOTES cholecystectomy as well. Due to the inability to triangulate, adequate exposure of the CVS cannot be reliably guaranteed. Consequently a safe pure NOTES cholecystectomy cannot be ensured with current endoscopic technology. By combining a transgastric approach with laparoscopic mini-instruments (2 mm) as described in **chapter 7**, cholecystectomy could successfully be performed as minimally invasive as currently possible in combination with maintenance of the ability to triangulate, and therefore maximal safety. In our opinion such a hybrid approach represents an essential safety bridge for all potential pure human NOTES procedures. This approach will also be studied in the AMC in a human protocol shortly.

Lessons should be learned from the introduction of laparoscopic cholecystectomy two decades ago. Laparoscopic cholecystectomy was introduced (too) fast, driven by media, patient demand, industry and physician competition. Initially, this led to an increased rate of bile duct injuries and consequently considerable morbidity. ²⁰ If intraperitoneal NOTES procedures are to become the even less invasive alternative to laparoscopic surgery it should be introduced safely and in a more controlled fashion. Starting with extensive experimental (animal) studies and training prior to human pilot studies.

At the start of the research presented in this thesis consensus existed that secure transluminal closure of the access site was the most fundamental challenge that needed to be surmounted before NOTES could be translated into human clinical trials. After thorough ex vivo and in vivo experiments by us (**chapter 5, 6 and 7**) and small human retrospective case series by others²¹⁻²³, the OTSC-system was selected for a human phase II study. In **chapter 12** we showed that the OTSC-system can achieve successful closure in the majority of patients with uncontrolled, unplanned, acute gastrointestinal perforations. These results can probably be extrapolated to planned, controlled perforations for endoscopic intraperitoneal NOTES procedures, starting with hybrid procedures under laparoscopic control.

It seems that the fundamental challenge of safe transluminal closure has been overcome. However, a randomized controlled trial comparing OTSC closure with laparoscopic closure should be performed to confirm these results. A randomized study comparing endoscopic versus surgical management of acute perforations will, however, require many more patients and will be very difficult to perform in view of the rarity of these complications. Nevertheless, we are currently preparing a randomized controlled multicenter trial comparing perforation closure using the OTSC-system with laparoscopic closure (CLIPPER II-trial).

The future of NOTES was uncertain at the start of the research presented in this thesis. In the past five years the NOTES-hype has gradually subsided and the future of NOTES may even be more uncertain than it was before. Pure intraperitoneal NOTES procedures are still not ready to be translated into human clinical trials. Nevertheless the quest for NOTES has brought surgeons and therapeutic endoscopists closer together and has been pivotal in delivering some technical advances in both endoscopy and surgery. Endoscopic closure of gastrointestinal perforations represents a successful spin-off of NOTES research from which patients will benefit and may lead to a paradigm shift with endoscopy replacing surgery as the first line of treatment in case of acute iatrogenic gastrointestinal perforations. Even if NOTES will not make it to a clinical accepted alternative to laparoscopic surgery, the road to NOTES has been very much worthwhile.

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