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Falk Workshop
GERD: Gastroesophageal Reflux Disease
September 5, 2013
Messe Congress Graz
Graz, Austria

Abstracts
Abstracts of Invited Lectures

Falk Workshop

GERD: GASTROESOPHAGEAL REFLUX DISEASE

Graz (Austria)
September 5, 2013

Scientific Organization:
A.J. Eherer, Graz (Austria)
G.J. Krejs, Graz (Austria)
R. Pointner, Zell am See (Austria)
CONTENTS

Session I

Early changes or “How does it all start”

Chair:
P. Malfertheiner, Magdeburg
R.C. Orlando, Chapel Hill

Epidemiology of GERD
G.J. Krejs, Graz

Esophageal and gastric motility and gastroesophageal reflux disease
G. Stacher, Vienna

GERD: Early mucosal changes:
– Endoscopy (No abstract)
F. Schreiber, Graz

– Histology
G. Gorkiewicz, Graz

Session II

Medical therapy

Chair:
A.J. Eherer, Graz
S.J. Spechler, Dallas

Can withdrawal of PPIs be accomplished? And what if PPIs fail?
O.B. Schaffalitzky de Muckadell, Odense

Helicobacter pylori and GERD (No abstract)
P. Malfertheiner, Magdeburg

Lifestyle modification and alternative approaches
A.J. Eherer, Graz
Session III

Surgical aspects

Chair:
L. Lundell, Stockholm
R. Pointner, Zell am See

Borderline indications and selection of patients. "Surgery better than medical therapy?"
L. Lundell, Stockholm 17 – 18

Management of operative failures – Does endoscopic therapy still have a future? (No abstract)
R. Pointner, Zell am See

Esophagitis: Is acid always the problem? (No abstract)
F. Hagenmüller, Hamburg

Does Barrett’s esophagus regress after surgery (or PPIs)?
S.J. Spechler, Dallas 19

Session IV

Neoplasia

Chair:
C. Ell, Wiesbaden
J. Zacherl, Vienna

Molecular steps to neoplasia in the distal esophagus
S.J. Spechler, Dallas 23

Endoscopic therapy of early neoplasia
C. Ell, Wiesbaden 24

How good is the neosquamous epithelium?
R.C. Orlando, Chapel Hill 25

Multimodal therapy: Esophageal cancer
J. Zacherl, Vienna 26 – 28

List of Chairpersons, Speakers and Scientific Organizers 29 – 30
Session I

Early changes or
“How does it all start”
Epidemiology of GERD

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While peptic ulcer disease was the most important acid-related disease in the last century, GERD has now taken its place. Fifty years ago GERD was not an important entity and the gastroenterology textbooks of the time gave it very little room. Today heartburn bothers 20 to 40% of the population. Seven percent complain of daily heartburn and 15% have it at least once a week. In the US (population 300 million) 15 billion dollars are spent per year for the evaluation and treatment of GERD. The increased and for some of the community alarming consumption of proton pump inhibitors (PPIs) may in large part be due to the need to control heartburn. In Austria (population 8 million) we use 230 million doses of PPIs per year, for an average 30 tablets per person including infants and children. The clear increase in the prevalence of GERD is most convincingly related to the pandemic phenomenon of more frequent overweight and obesity. All the features of metabolic syndrome (BMI, hypertension, hyperglycemia and hypertriglyceridemia) are significantly correlated to the prevalence of GERD. Several other risk factors for GERD have been identified: hiatal hernia has gone and returned, use of NAISDs, and playing of wind instruments, among others. The latter is controversial since breathing exercise may enhance sphincter competence (see Dr. Eherer’s contribution). GERD prevalence does not increase with higher age but patients who have GERD may suffer more as they age. Based on meta-analyses the prevalence of GERD does not increase after eradication of Helicobacter pylori. Consequences of reflux disease have also increased: Barrett’s esophagus has become a leading subject for clinical research and the incidence of adenocarcinoma of the distal esophagus has increased 5-fold in the last 40 years.
The extent of esophageal acid exposure is attributable to a variety of factors. Investigations using multiple regression analyses revealed that acid exposure correlated strongly with low resting pressures of the lower esophageal sphincter (LOSP), presence of a hiatal hernia, short intra-abdominal portion of the sphincter, low distal esophageal contraction amplitudes and impaired clearance of refluxed materials. We assessed, using multiple regression analyses, the roles of LOS, esophageal contractile and transport function in upright and recumbent postures as well as hiatal hernia, age, sex and body mass for esophageal acid exposure and esophagitis. In 116 patients with reflux symptoms, acid exposure was recorded by 24-hour pH monitoring, motility manometrically, bolus transport (supine) scintigraphically, hiatal hernia and esophagitis endoscopically. In upright as well as in recumbent posture, acid exposure increased significantly with lower LOSP and lower distal esophageal amplitudes. Stepwise backward multiple regression analyses revealed that in upright posture body mass, distal esophageal contraction amplitude and esophageal transport velocity predicted most accurately the extent of acid exposure, whereas in recumbence acid exposure was predicted best by the percentage of effective contraction waves and male sex. The variables best predicting occurrence and severity of esophagitis were transport in recumbence and male sex. In an earlier study employing multiple linear regression analysis we evaluated the impact of the rate of gastric emptying on 24-hour and on 2-hour postprandial acid exposure in relation to the impact of LOSP and esophageal contractile and clearance function in 71 patients with symptoms suggestive of both delayed emptying and reflux. It was revealed that slow proximal, but not total, gastric emptying of a radio-labelled semisolid meal contributed, although markedly less than low LOSP, significantly to both 24-hour and postprandial acid exposure. No relationship was found between gastric emptying and LOSP or esophageal motility. Controlled trials investigating the effect of therapies combating esophageal and gastric motor dysfunction on reflux activity have not yet been undertaken.
GERD: Early mucosal changes – Histology

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Prolonged (i.e. chronic) reflux of fluid from the stomach containing acid, pepsin and unconjugated bile acids leads to damage of the stratified squamous epithelium of the esophagus in GERD. This leads to adaptations of the esophageal mucosa at the cellular and tissue level which are visible histologically. Especially in cases wherein erosions/ulcerations are endoscopically not visible these changes are key to the diagnosis of GERD and are therefore important for the prevention of its sequels (i.e. Barrett esophagus and adenocarcinoma). Dilated intracellular spaces in-between the individual squamous epithelial cells indicate the direct toxic effect of the refluxate on the cells, whereas increased intraepithelial lymphocytes, eosinophils and neutrophils are signs of the immune reaction subsequent to tissue damage (i.e. inflammation). Basal cell hyperplasia and elongation of the papillae of the squamous epithelium are regenerative signs of this chronic mucosa damage. Moreover, prolonged reflux leads to columnar metaplasia of the esophageal squamous epithelium, wherein the resident squamous epithelium is replaced by a mucinous columnar epithelium, histologically visible in its early stages by the so-called multilayered-epithelium (ME). If GERD persists columnar metaplasia may progress into intestinal metaplasia (i.e. Barrett esophagus), wherein the columnar epithelium transforms into an intestinal or colonic type epithelium, the hallmark histological change in this condition is the presence of mucin-producing goblet cells. Consequently intestinal metaplasia may lead to the development of adenocarcinoma of the gastro-esophageal junction in GERD (the so-called “reflux-columnar metaplasia-adenocarcinoma sequence”).
Session II

Medical therapy
Can withdrawal of PPIs be accomplished? And what if PPIs fail?

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**Background:** Longitudinal studies and current understanding of GERD indicate that it is a chronic disease with a high prevalence. PPIs are the mainstay and a major advance in the treatment, and accordingly the consumption of PPIs is high. However, use of PPI is increasing and the drug probably overprescribed. At the same time it has become evident that a substantial number of patients fail to respond to PPI. The definition of GERD has varied between studies and over time. Furthermore, entities as non-erosive reflux disease (NERD) and functional heartburn has come into focus and pathophysiology of GERD in patients from daily practice may not be similar to the pathophysiology in patients included in original studies on management of GERD. Previous studies suggest that relapse occurred in most patients after stopping PPI, especially in patients with erosive esophagitis.

**Withdrawal of PPI**

In a recent study we aimed to investigate if patients on long-term acid suppressing therapy needed continued treatment to control symptoms.

**Methods:** In a double-blind study in long-time users from general practice patients were randomized to esomeprazole 40 mg or placebo. Patients with alarm symptoms, endoscopically verified esophagitis or ulceration, or ongoing use of anti-inflammatory drugs were excluded. Primary endpoint was time to discontinuation due to insufficient control of symptoms.

**Results:** 171 patients were included. At 12 months 62/86 (73%) in the placebo group and 18/85 (21%) in the esomeprazole group had discontinued.

**Conclusion:** Results from literature as well as our results suggest that PPIs can be withdrawn in some patients with less severe disease. However data on the optimal strategy for discontinuation is lacking and the possibility of acid rebound – as demonstrated in normal persons – has not been studied in details.

**GERD that does not respond to PPI**

Causes of lack of response include wrong diagnosis (functional dyspepsia?), functional heartburn, inadequate compliance or dosing and non-acid reflux. The management depends on whether the initial diagnostic work-up was based on subjective symptoms or objective findings. Additional diagnostic tests include endoscopy and mucosal biopsy, ambulatory 24 h esophageal pH/impedance monitoring and Biltec. pH/impedance monitoring seem to be the most useful test, however although theoretically attractive, the predictive value of these tests remains to be demonstrated. Due to the diverse causes treatment should be individually tailored. Increased PPI-dosage, reduction of transient lower esophageal relaxations, surgery or visceral pain modulators should be considered.
Lifestyle modification and alternative approaches

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The first step in management of gastro-esophageal reflux disease is lifestyle modification. This includes dietary recommendations such as increasing fibre intake and lowering of dietary fat. Whereas some physiological evidence exists that various food products as well as alcohol and tobacco effect the pressure of the lower esophageal sphincter, none of these agents proofed in a clinical trial a beneficial role. Thus, it is generally recommended to avoid food items that trigger GERD symptoms in the experience of the patient. Weight loss in patients who are obese and the advice to elevate the head of the bed are the only procedures with some degree of scientific evidence to effect reflux disease. As a result of many discussions with close friends being musicians and singers who questioned the scientific literature that opera singers are at a high risk to develop reflux disease we developed a training program that induces a change from thoracic to abdominal breathing. We hypothesized that this change in breathing actively trains the diaphragm, and thus potentially strengthens the LES. In a randomized trial using breathing exercises as the intervention we could show an improvement of gastroesophageal reflux, assessed by quality of life, pH-metry and PPI use. Although it is easier to swallow PPIs than to perform physical training at least for a subgroup of highly motivated patients who resent drug ingestion a structured physical exercise could offer a new approach to their problems.
Session III

Surgical aspects
Borderline indications and selection of patients. 
"Surgery better than medical therapy?"

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Albeit that the pathogenesis of GERD is multifactorial, impaired lower oesophageal sphincter (LOS) function occupies a pivotal role both in the resting state to prevent reflux but primarily so as reflected by the reponse of the LOS to gastric stimulation. The resulting incomplete capacity for reflux prevention, in the gastro-oesophageal junction area, leads to abnormal reflux of gastroduodenal contents both in the upright and supine body position. Modern medical therapies are totally constrained to the control of the acid component of the refluxate. In chronic erosive GERD antireflux surgery (ARS) has proven to be very efficacious and superior when compared to the results of traditional medical therapies, such as H2-blockers. However, with the introduction of proton pump inhibitors (PPI) medical therapy was substantially improved. Despite this, treatment failures are inevitable irrespective of which of these two effective therapies that is chosen. For instance there seems to be a positive correlation between the increased failure rate and the duration of the observation period but an inverse one between the recurrence of the disease and the dose of PPI therapy.

During recent years some reports have presented data from comparative trials between ARS and PPI demonstrating outcomes that are somewhat conflicting. The reasons for this may be found in differences in trial designs and also in the structure and content of the therapeutic strategies that are compared. The study with the by far longest clinical follow up is the SOPRAN study comparing open ARS and omeprazole (ome). This study protocol contains a follow up period covering more than a decade and the clinical outcomes have recently been published. There has always been a concern about the durability of reflux prevention offered by surgery or as well as PPI therapy. It is likely that a marker for an emerging risk for recurrence of GORD is abnormal acid reflux as assessed by ambulatory 24-hour pH-metry. The LOTUS trial compared maintenance therapy provided by esomeprazole (dose-adjusted when required), with standardized laparoscopic antireflux surgery in patients who respond well to acid suppressive therapy. We hereby report the final results of the 5 year follow-up for the LOTUS study.

Direct comparisons between surgical and medical therapies are of major importance when evaluating treatment options in chronic GERD, but have seldom been performed with adequate design and duration of follow-up. Such comparisons must include objective measurements of pathophysiological mechanisms, including 24-hour pH-metry, which quantifies the exposure of the oesophageal mucosa to harmful refluxate. pH-metry has higher diagnostic sensitivity for GERD than endoscopy and reflects the efficacy of acid reflux control if performed during therapy. We had the opportunity to perform pH-metry during a large, randomized study between LARS and esomeprazole use, performed at selected high-volume centres in Europe, with pH-metry data available from around 64–76% of patients. The published clinical data show no significant difference in terms of treatment failure between medical and surgical therapies up until 5 years of follow-up. This large, multicenter, randomized trial indicated that with modern forms of anti-reflux therapy, either by drug-induced
acid suppression or after LARS, most patients remain in remission for at least 5 years. LARS proved to be more beneficial than drug therapy on a number of secondary outcome measures. Of utmost importance is the fact that both treatments were well tolerated, with no surgery-related mortality and no concern regarding long-term use of esomeprazole. In a recently published UK trial results were demonstrated to show the superiority of LARS as compared to conventional PPI therapy.
Does Barrett’s esophagus regress after surgery (or PPIs)?

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Barrett’s esophagus is the result of metaplasia, the process in which one adult cell type replaces another. Metaplasias often are the result of chronic inflammation and chronic reflux esophagitis appears to cause the squamous-to-columnar metaplasia of Barrett’s esophagus. The precise mechanisms underlying this process remain unclear, however. One popular hypothesis holds that Barrett’s metaplasia is the result of transcommitment, in which progenitor cells in the esophagus that normally would differentiate into squamous cells instead differentiate into columnar cells in the setting of gastroesophageal reflux. Recent research in animal models has suggested that Barrett’s metaplasia might result from the upward migration of stem cells from the gastric cardia, or from the expansion of a nest of residual embryonic cells located at the gastroesophageal junction. In a rat model of reflux esophagitis, Barrett’s metaplasia appears to occur when stem cells from the bone marrow are transported through the blood to the damaged esophagus, where they differentiate into columnar cells. It is not clear which, if any, of these proposed mechanisms underlies the development of Barrett’s metaplasia.

In theory, metaplasias are potentially reversible if the underlying inflammatory process is eliminated. Experience with endoscopic ablation provides unequivocal evidence that Barrett’s metaplasia is reversible if the metaplastic mucosa is destroyed and then allowed to heal while reflux esophagitis is prevented either with PPIs or with antireflux surgery. It is less clear whether elimination of reflux esophagitis alone (without ablation) is sufficient to cause Barrett’s metaplasia to revert to squamous mucosa. Surveillance endoscopy in patients on PPI therapy often reveals the development of squamous islands in Barrett’s metaplasia, but these islands might be the result of the biopsy procedures, which essentially ablate a segment of Barrett’s metaplasia, rather than just the healing of reflux esophagitis. Although a number of reports have alleged that Barrett’s metaplasia can regress or even disappear entirely with successful antireflux surgery or PPI therapy, it is often difficult to exclude biopsy sampling error as the cause of the apparent regression. The bulk of the evidence suggests that partial regression of Barrett’s metaplasia with antireflux surgery does occur frequently, whereas complete regression occurs infrequently, if ever. The more important question is whether successful antireflux treatment prevents the development of cancer in Barrett’s esophagus. Despite plausible arguments that antireflux surgery should be better than PPIs for cancer prevention, high-quality, long-term studies find no difference in cancer incidence between patients with Barrett’s whose GERD is treated medically and those whose GERD is treated surgically.
Session IV

Neoplasia
Molecular steps to neoplasia in the distal esophagus

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To develop a cancer in Barrett’s esophagus, the metaplastic cells must accumulate a series of genetic and epigenetic alterations that endow them with the physiological hallmarks of malignancy proposed by Hanahan and Weinberg in 2000, which include self-sufficiency in growth signals, insensitivity to anti-growth signals, the ability to evade apoptosis, the acquisition of limitless replicative potential, the ability to sustain angiogenesis, and the abilities to invade and metastasize. In addition, the cells must reprogram their energy metabolism to support the extensive proliferation required of tumor cells, and they must evade destruction by immune cells. Numerous genetic alterations that might affect these abilities have been described during the neoplastic progression of Barrett’s esophagus. Conceptually, it is useful to classify an alteration according to the major physiologic cancer hallmark that it endows.

The expression of oncogenes (e.g. cyclin D1, K-ras), growth factors (e.g. TGF-α), and growth factor receptors (e.g. EGFR) enable Barrett’s cells to acquire self-sufficiency in growth signals. Insensitivity to antigrowth signals occurs primarily through the inactivation of tumor suppressor genes (e.g. TP53 and p16). Inactivation of TP53 also enables cells to evade apoptosis. Reactivation of the enzyme telomerase can give cells limitless replicative potential. Angiogenesis can be sustained by the expression of angiogenic factors such as vascular endothelial growth factor (VEGF). To invade and metastasize, the neoplastic cells must dissociate themselves from surrounding cells by disrupting cell adhesion proteins such as the cadherins and catenins, and by degrading the extracellular matrix through the secretion of matrix metalloproteases.

In Barrett’s esophagus, the acquisition of these physiological hallmarks of malignancy is facilitated by genomic instability, manifested as gains or losses in segments of chromosomes that alter cellular DNA content. Aneuploidy, the condition in which there is abnormal cellular DNA content, can be detected by flow cytometry, by fluorescence in situ hybridization (FISH), and by automated image cytometry. Aneuploidy has been proposed as a biomarker for neoplastic progression in Barrett’s esophagus, as have a number of the genetic alterations listed in the preceding paragraph. Although there have been some promising preliminary studies, molecular biomarkers are not yet ready for routine clinical use in patients with Barrett’s esophagus.
Endoscopic therapy of early neoplasia

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Non-neoplastic Barrett epithelium is a contraindication for endoscopic therapy. Neither endoscopic resection (ER) nor endoscopic ablation (EA) by means of radio frequency or argon plasma coagulation is allowed. Endoscopic therapy has to be restricted to neoplastic Barrett epithelium. In low grade interepithelial neoplasia (LGIN), proven by a second pathologist as true neoplastic lesion, ER is the best way to remove the lesion and to get a safe pathological judgement. Only if the lesion can not be localized, ablation therapy is allowed. The other option is, to have a short control interval until the LGIN can be localized; then ER follows. In high grade interepithelial neoplasia (HGIN) ER is mandatory, since in almost all cases of HGIN mucosal or even submucosal invasive cancer can be detected. When biopsy detects already cancer the staging should also contain endosonography to exclude lymphnode metastases. Standard ER techniques are the "lift and cut" techniques using a ligation or a cap. Actually, there is no place for endoscopic submucosal resection (ESD).

After complete resection of all neoplastic lesions thermal ablation of the non-neoplastic Barrett is mandatory, otherwise a tumor recurrence of up to 40% within the next 2–3 years has to be expected. In short segmented Barrett (SSBE) APC ablation is the ablation technique of choice; in LSBE radiofrequency ablation can be used.

Long term results in mucosal Barrett cancer treated in Wiesbaden by ER followed by EA for the non-neoplastic Barrett in 1000 patients has shown, a long time complete remission rate of 95%. Therefore all other treatment options, especially surgical resection, are methods of reserve. In addition also so called "low risk submucosal" cancer infiltrating the first third of the submucosal layer should be treated endoscopically with curative intention before surgery is considered.

Summarizing the evolution of endoscopic treatment it became clear within the last 10 years that ER is the best, the safest und the most convenient treatment option in early Barrett cancer.
How good is the neosquamous epithelium?

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Endoscopic radiofrequency ablation (RFA) of dysplastic Barrett's esophagus combined with proton pump inhibitor therapy is commonly utilized for preventing progression of dysplastic BE to esophageal adenocarcinoma. Fundamental to the success of this approach is the healing of the areas ablated of Barrett’s esophagus with a stratified squamous epithelium referred to as ‘neosquamous epithelium (NSE)’ to distinguish it from native esophageal stratified squamous epithelium. Although NSE appears ‘normal’ endoscopically, the re-emergence of Barrett’s esophagus over time in the same ablated segment raises the question of the health and durability of NSE. Moreover, these concerns are supported by recent published data showing that NSE possesses defective barrier function and that the defective barrier persists while on proton pump inhibitors and this is the case even long after sufficient time has passed on proton pump inhibitors for healing to take place from prior ablation. Notably, one such defect identified within NSE is the down-regulation of claudin-4, a protein localized to the tight junction. How this abnormality contributes to vulnerability of NSE to destruction and the re-emergence of Barrett’s esophagus is reviewed and discussed in light of current knowledge about the barrier function of healthy esophageal squamous epithelium.
Multimodal therapy: Esophageal cancer

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Introduction: After disappointing results of postoperative chemotherapy (CTx) and/or radiotherapy to increase the chance of long term survival after resection for esophageal cancer (EC) in the 80ies multimodal treatment was adopted preoperatively. The aim of preoperative treatment is to enhance the chance of complete resection, which is a very strong and potentially influencable prognostic factor in surgery for EC. Preoperative treatment of locally advanced EC gained popularity in the last 2 decades since remarkable clinical response had been observed in various phase-II studies and case series. However, scientific evidence for survival benefit was absent until the presentation of positive results of randomized controlled studies.

Method: Results of randomized controlled studies on neoadjuvant treatment of EC and AC of the esophagogastric junction are presented.

Results: The first positive large scale study of neoadjuvant CTx (cisplatin/5-FU) was published in 2002 by the MRC group [1]. The MRC study showed a significant survival benefit at 2 years (43% vs. 34%) after neoadjuvant CTx among potentially resectable esophageal squamous cell cancers (SCC) and adenocarcinomas (AC). In the following years 2 randomized studies (MAGIC, FFCD) evaluating perioperative CTx (cisplatin/5FU based combination) for esophagogastric cancer (AC) were presented with concordant results showing a significant survival advantage in the treatment group (periop. CTx and resection) over the control group (surgery alone) [2, 3]. One further randomized trial was performed in Germany (EORTC) and compared neoadjuvant CTx + surgery vs. surgery alone for ACs of the esophagogastric junction [4]. The trial had to be closed prematurely due to poor accrual. As a consequence of incomplete accrual the survival benefit of the experimental arm was not significant but the crude results accordingly confirmed the findings of the studies on perioperative chemotherapy – MAGIC and FFCD.

As a disadvantage it may be mentioned that the complete postoperative protocol was administered in a minority of the patients undergoing the perioperative schedule due to toxicity and clinical intolerance [2, 3].

Recently, the results of the first randomized trial (CROSS Trial) comparing neoadjuvant radiochemotherapy (RCTx) plus resection with surgery alone in EC revealed a remarkable survival benefit after neoadjuvant RCTx [5]: The 5-year survival rate after multimodal treatment was 47% vs. 34% after surgery alone (hazard ratio 0.67; CI 0.49–0.87). Histopathological response was very impressive especially in SCC (47%).

While reading the overall results of the mentioned studies one has to keep in mind that the inclusion criteria, tumour localisations, histological types and surgical procedures were different and each study should be interpreted individually.
Numerous studies demonstrated that only responders to neoadjuvant treatment experienced a survival benefit, whereas non-responders might have an even worse prognosis compared with patients who underwent surgery without any preoperative treatment. Additionally, preoperative RCTx was repeatedly reported to increase postoperative morbidity, while neoadjuvant CTx does not seem to influence morbidity. In 2 randomized trials comparing full dose RCTx with neoadjuvant RCTx and surgery even hospital mortality after esophageal resection was dramatically increased (up to 12%) in the RCTx and surgery groups. These observations – bad prognosis of non-responders and potentially increased perioperative risk – cause a remarkable therapeutic dilemma and stimulate research to identify predictive markers and to make surgery safer. It is encouraging that some groups were able to adopt neoadjuvant RCTx without observing an obvious raise of adverse postoperative events.

Currently, only one incomplete study is available which compared neoadjuvant CTx and RCTx in AC of the esophagogastric junction and distal esophagus [6]: Although the study was closed early and the survival benefit of RCTx did not reach significance, the results indicate a survival advantage of neoadjuvant RCTx. However, also in this study postoperative mortality in the RCTx arm was very high (10.2%).

Conclusion: Summing up, neoadjuvant treatment is recommended in locally advanced (T3, T4, each N+) potentially curative resectable EC. RCTx may have a greater influence on prognosis than CTx and is also effective in AC. In risk patients and clearly resectable stages (especially in AC) neoadjuvant or perioperative CTx may be preferred due to the higher postoperative risk after RCTx.

The burning questions currently are: How may responders/non-responders be identified to tailor the treatment? Which treatment options may be of benefit for non-responders to established neoadjuvant treatment? Is surgery still necessary after RCTx in responders, especially in supracarinal SCC? How to identify complete responders?

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Falk Workshop

GERD: Gastroesophageal Reflux Disease

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Innovative Drugs
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