The Rationale and Efficacy of Primary and Secondary Prevention in Adenocarcinomas of the Upper Gastrointestinal Tract

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Abstract

While the primary risk factor for oesophageal adenocarcinoma (OAC) and its precursor lesion Barrett's oesophagus (BO) is gastro-oesophageal reflux, the infection with *Helicobacter pylori* (*H. pylori*) is the dominant risk factor for gastric cancer. Reduction of reflux by dietary measures and proton pump inhibitors has some merits in OAC prevention, and the chemopreventive effect of Aspirin and statins is being widely investigated; however, improved outcome in OAC occurs primarily as the result of secondary prevention. Early detection of neoplastic lesions in Barrett's metaplasia can be achieved by surveillance endoscopies. Novel endoscopic imaging modalities carry similar importance as the endoscopic treatment techniques as without detection of early lesions, therapy cannot be applied. Minimally invasive approaches

are currently being investigated to identify patients with BO who are at particular risk of neoplastic progression. While dietary factors also play an important role in the prevention of gastric cancer and chemoprevention seems to be promising, the most beneficial effect has been shown for the eradication of *H. pylori* infection, which results in at least a one third reduction of gastric cancer risk. This effect can be further improved if the eradication takes place prior to the development of pre-neoplastic gastric conditions such as mucosal atrophy or intestinal metaplasia (IM). The definition of the "point of no return", after which eradication is less effective, is of high importance, although *H. pylori* eradication can still be beneficial even at more advanced stages of mucosal changes. For this reason, patients with advanced atrophy and IM should undergo endoscopic surveillance in the same way as patients with BO. There is also need for development of non-invasive tests to identify patients at high risk of progression to gastric cancer to improve outcome of these surveillance approaches.

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Oesophageal Adenocarcinoma

Trends in the incidence of oesophageal squamous cell cancer and adenocarcinoma are changing in the Western world. Oesophageal adenocarcinoma (OAC) has become the predominant type with a constant rise in incidence over the last 30 years [1–3]. OAC is associated with chronic gastro-oesophageal reflux of acid and bile and Barrett's metaplasia is the well-established precancerous condition [4]. Unfortunately, 95% of patients are not known to have Barrett metaplasia at the time of OAC diagnosis [5]. Risk factors for OAC include age >50 years, male gender, obesity, smoking and Caucasian ethnicity [6]. Measures of primary prevention focus on diet and reflux control in those with symptoms, but there are no strategies for general screening. Secondary prevention aims at early detection of dysplastic lesions and OAC within the framework of endoscopic surveillance of Barrett's oesophagus (BO) and endoscopic treatment of early dysplastic lesions.

Primary Prevention

Gastroesophageal Reflux

Although the association of pathological gastro-oesophageal reflux and development of Barrett's oesophagus has been clearly established, further factors play a role in the progression of BO towards neoplasia [5]. Identification of patients at risk is still a major issue since progression towards dysplasia and cancer does occur also in absence of classic reflux symptoms [7]. However, intensity, frequency and duration of chronic reflux symptoms remain important risk indicators for progression. A Swedish case-control study showed an OR of 2.0 for cardia cancer and of 7.7 for distal oesophageal cancer in patients with recurrent reflux symptoms compared to patients without symptoms. A higher prevalence of reflux symptoms in patients with cancer in the distal oesophagus or at the gastro-oesophageal junction (GOJ) compared to controls was also reported in studies from the United States [8, 9]. Another population-based case-control study from the United States showed an OR for OAC of 3.61 (95% CI 2.49–5.25) in the presence of reflux symptoms, of 5.85 (95% CI 3.18–10.75) in case of a hiatus hernia and of 8.11 (95% CI 4.75–13.87) in case of both factors being present [10]. There is a clear need for non-invasive tools for identifying patients at risk who do not present with typical symptoms [5, 11]. Blood-based markers would be most feasible regarding clinical applicability. There are also efforts to assess the usefulness of breath tests for analy-

sis of volatile markers as well as community-based application of minimally invasive sponge- or brush-based techniques.

Chemoprevention

Exposure of the distal oesophagus to gastric acid and bile induces chemical irritation and a local inflammatory reaction. Bile salts, in particular, display properties that interfere with the barrier function of cell membranes and with damage to DNA by increase of intracellular radical oxygen species. A modified local immune response may also contribute, as exposure to bile has led to acceleration of carcinogenesis in the experimental setting in mice [12].

A meta-analysis of 7 observational studies including 2,813 Barrett's patients and 317 patients with OAC showed a significantly protective effect by use of proton pump inhibitors (PPI; OR 0.29; 95% CI 0.12–0.79). This effect is not shown for histamine 2 receptor antagonists (H2RA) [13]. A nested case-control study in more than 1,000 US Veterans confirmed this effect, which was even more obvious with higher doses of PPI (OR 0.11; 95% CI 0.04–0.36) [14]. Recently, the effect of PPI on the prevention of further progression of BO has been prospectively assessed in the AspECT trial [15]. A total of 2,557 patients were recruited in 84 UK centres and one in Canada before randomisation in a 2-by-2 factorial design to assess the long-term effect of Esomeprazole (20 vs. 40 mg) each with or without Aspirin (300 mg). The primary endpoint of this study was a composite of time to all-cause mortality, incidence of OAC and of high grade dysplasia (HGD), all adjusted for age, length of the Barrett's segment and presence of intestinal metaplasia (IM). During a median follow-up time of 8.9 years, 313 primary events occurred. High-dose PPI (40 mg Esomeprazole) was superior to low dose (20 mg) with regards to protection from dysplastic or neoplastic lesions. The use of Aspirin was beneficial only when patients with the use of further NSAIDs at inclusion were censored. The combination of high dose PPI plus Aspirin showed the best outcome regarding chemoprevention of BO and the complications mentioned above as included in the composite primary endpoint [15]. The number needed to treat to prevent a primary event was 34 for PPI and 43 for Aspirin. An effect for other NSAIDs could not be confirmed [14, 16].

A protective effect against the development of BO has also been attributed to statins. A case-control study and consecutive meta-analysis by Beales et al. [17] showed a risk reduction by nearly 40% for statin users (OR 0.62; 95% CI 0.37–0.93). The effect was even stronger when

statins were combined with Aspirin (OR 0.43; 95% CI 0.21–0.89). These results were similar to a case-control study investigating the protective effect of statins against the development of OAC in US Veterans with BO, furthermore confirming a dose-dependent effect [18]. The effect on protection against BO was more pronounced in obese patients [19].

Other candidate drugs proposed for prevention of OAC, such as metformin, have not been confirmed to have a beneficial effect [20–22].

Obesity

Obesity is a definite risk factor for OAC (relative risk 2.73; 95% CI 2.16–3.46) [23]. A meta-analysis of observational studies demonstrated a risk increase for cardia cancer by 50% in Western populations (OR 1.55; 95% CI 1.31–1.84) [24]. There is a positive correlation between the risk of cancer at the GOJ and increasing BMI [25]. In contrast, recent data from the EPIC trial showed no association between OAC and BMI or waist circumference, but a positive result for hip circumference [26]. Observations from the Chinese Linxian cohort, which included almost 30,000 individuals showed a decreased risk for non-cardia gastric-cancer, but no association with cardia cancers (usually referring to Siewert type 2 and 3 cancers at the GOJ) [27]. Nevertheless, obesity is an established risk factor for chronic gastro-oesophageal reflux disease and therefore likely to contribute to oesophageal carcinogenesis.

Secondary Prevention

Secondary prevention refers to approaches that enable the early detection of neoplastic lesions, which leads to curative – and often minimally invasive – treatment. BO and its endoscopic surveillance, similar to colonic polyp surveillance, is an excellent example of an effective strategy.

Surveillance of BO

Endoscopic surveillance of patients with BO is the key to improving outcome. The absolute risk of progression of BO to OAC is very low (0.2–0.7% per patient per year) [28–30]. There is an established association of the length of BO and its risk of progression. Data from 1,175 patients who were followed-up at 5 tertiary centres in the United States demonstrated a risk increase of 28% per each additional cm of Barrett's length [31]. A study by Pohl et al. [32] showed transition rates towards more advanced lesions in 0.22% of patients with segments ≥ 3 cm, 0.03% in patients with segments ≥ 1 cm and < 3 cm, and 0.01 if the metaplastic segment was < 1 cm. This resulted in a calcu-

lated number-needed-to survey of 450 for segments > 3 cm, 3,440 between 1–3 cm and 12,364 if the area was < 1 cm. There is also evidence that the length of BO is established at index endoscopy and does not change over time [33].

The risk of progression towards invasive neoplasia increases substantially with presence of dysplasia. While there are conflicting results for lesions “indefinite for dysplasia” and low grade dysplasia (LGD) [30, 34, 35], the progression rates increase to 25% when HGD is present [36].

Endoscopic surveillance at regular intervals aims to increase the proportion of patients in whom neoplastic lesions are detected at an early stage, that is, HGD or early cancer that is confined to the mucosa so that curative, endoscopic treatment can be given. However, the intervals and strategies vary between countries, mainly due to contradictory evidence in terms of the benefits of surveillance. Corley et al. [37] could not confirm a significantly reduced risk of death from OAC associated with surveillance (adjusted OR 0.99; 95% CI 0.36–2.75), disagreeing with previous studies. However, a meta-analysis of 51 studies including more than 11,000 patients, demonstrated that endoscopic surveillance of patients with non-dysplastic BO increases the likelihood for early detection of neoplastic lesions and therefore reduces mortality by more than 61% (mortality risk 0.386; 95% CI 0.242–0.617) [38]. In a multicentre prospective cohort ($n = 783$), 53 patients developed HGD or OAC during surveillance with OAC being diagnosed at an earlier stage compared to diagnosis in the general population ($p < 0.001$) [39]. Patient-related factors (e.g., Barrett's length, histopathological characteristics) need to be taken into account to further tailor individual risk-adapted surveillance intervals. The so-called Seattle protocol suggests that targeted biopsies be taken from visible lesions suspicious for dysplastic changes of the mucosa, as well as 4 “random” quadrant biopsies be taken at 2-cm intervals over the entire extent of the Barrett's segment [40].

The recent statement of the European Society for Gastrointestinal Endoscopy recommends surveillance every 3 years for patients with segments of 3–10 cm and every 5 years for those with a Barrett's length of 1–3 cm. Metaplastic segments < 1 cm should not be subject to surveillance [41]. If the segment exceeds 10 cm, then the patient should be referred to a specialised centre. This is also the case if endoscopic treatment is required. These specialised centres are defined by an annual case load of more than 10 new patients requiring endoscopic treatment of HGD and early OAC per year, a number of 30 supervised

endoscopic resections per year, specific Barrett's MDTs and an adequate database. Endoscopists and histopathologists should have undergone specific training [41]. It is of note that any degree of dysplasia (both LGD and HGD) requires confirmation by a second expert GI pathologist.

Endoscopic Treatment of Precancerous and Early Neoplastic Lesions

Dysplasia (confirmed LGD and HGD) and early cancer in the distal oesophagus need to be removed after discussion at a multidisciplinary team meeting. This is best achieved by a multimodal endoscopic approach with endoscopic mucosal resection of any visible lesion, followed by ablation of the remaining Barrett's segment. As recommended by national and European guidelines, the current gold standard for mucosal ablation is radiofrequency ablation, but for small segments argon plasma coagulation can be used [41, 42]. This strategy is both safe and effective resulting in minimally invasive treatment at early stage and thus fewer patients dying from OAC [43–46]. Treatment of LGD can be recommended under certain conditions, since it can be associated with significant progression rates. It is vital that LGD is confirmed by at least 2 independent expert pathologists as already indicated above [47, 48].

Endoscopic follow-up of patients even after complete eradication of the dysplastic/metaplastic segment is recommended in current guidelines [41, 49, 50]. Buried glands and recurrence of metaplasia can thus be detected and treated early [51, 52].

Advanced Endoscopic Imaging

Sampling error from random biopsy sampling according to the Seattle protocol carries significant limitations, mostly due to the fact that only a small area of the metaplastic segment can be assessed with these small tissue samples. The use of more sophisticated endoscopic techniques for the assessment of the Barrett's mucosa is encouraged. They include narrow band imaging or autofluorescence imaging for targeted biopsies of suspicious areas that might otherwise have been missed. There are also ongoing efforts to improve risk stratification by established standard methods of virtual chromoendoscopy and magnifying endoscopy [53]. Combination with Histopathological/molecular markers should then further increase the amount of information that enables further tailored surveillance (e.g., p53, p16, cyclin A and altered ploidy) [54, 55].

Similarly, confocal laser endomicroscopy allows the real-time detection of intestinalised epithelium and even dysplastic changes and this can also be combined with tis-

sue based biomarkers, resulting in excellent performance compared to standard histopathology [56, 57]. An alternative approach to classical tissue-based assessment of biomarkers is the application of molecular probes that can be viewed during endoscopy in real-time. One such approach takes advantage of the altered glycosylation patterns of the mucosal surface during the progression towards cancer which can be imaged with a fluorescent lectin [58]. However, these techniques are not yet ready for routine clinical practice and are mainly explored at academic centres.

New Approaches

New approaches utilise techniques that enable more “universal” sampling of the Barrett's mucosa to minimise sampling errors. Brushing techniques were combined with computer-assisted read-out systems (EndoCDx[©] system) to increase the diagnostic yield and more consistent inter-observer agreement [59, 60]. Prospective assessment of this technique in 1,266 patients showed an increase in the detection rate for dysplasia of 87.5% compared to usual biopsy sampling approaches [61] resulting in a number-needed-to-test of 9.4 to detect one additional case with dysplasia [62].

Another sampling device that does not require endoscopic access of the lower oesophagus is the Cytosponge[™]. This device is densely folded in a resolvable capsule that is swallowed and can then be retrieved by the string that is attached to it. While being retrieved, it gently scrapes the oesophagus collecting cells that can then be processed and evaluated. A prospective study in 1,110 patients showed sensitivity for BO of 79.9% (87.2% for segments >3 cm) and a specificity of 92.4%. A combination with certain tissue markers also allows assessment for dysplasia [63]. This approach is safe and well accepted by patients, and may well be cost effective for community-based screening [64–67].

Gastric Adenocarcinoma

Gastric cancer is a multifactorial disease and factors relating to immune response, diet and further environmental influences need to be balanced to maintain functional integrity of a healthy stomach [68]. Incidence rates of gastric cancer are decreasing (mainly in Western countries), but in spite of this, gastric adenocarcinoma remains a major health burden world-wide with nearly 2 thirds of new cases occurring in China, Japan and Korea. It is the third most common reason for cancer-related death, showing figures close to those for hepatocellular cancer, which

ranks second [69]. In 2012, more than a quarter of the 951,000 gastric cancers were located at the GOJ (which includes the cardia). GOJ cancers show the most dramatic increase in incidence over the last 50 years [70]. The global incidence rates were 3.3/100,000 for cardia cancers and 8.8/100,000 for non-cardia gastric cancer. Since most are diagnosed at an advanced stage, when only limited treatment options can be offered, there is imminent need for better means of prevention and early detection.

Primary Prevention

Diet

Alimentary factors have an impact on gastric cancer risk. Most evidence is available for high salt diets. Ingestion of salt in experimental animal settings causes gastritis by destroying the mucosal barrier leading to inflammation and damage such as diffuse erosion and degeneration [71–75]. A large number of human studies, including case-controls studies and prospective observational studies, confirmed the risk of high salt food in gastric carcinogenesis [76–80]. N-nitroso compounds (NOCs) are potent carcinogens and humans are exposed to various dietary NOCs by consumption of tobacco and even drinking water from certain sources [81]. NOCs are formed in vivo by the nitrosation of amides or amines in the stomach by nitrites. Nitrosamines are mainly found in cured meat products, smoked preserved food, and pickled and salt-preserved food [82]. Meta-analyses confirmed a positive association between tobacco consumption and an increased risk for gastric cancer. After smoking cessation, it takes about 10 years for the risk to return to that of the general population [83, 84]. However, studies conducted with the inclusion of *Helicobacter pylori* (*H. pylori*) found that, only in the presence of *H. pylori* gastritis, were these other environmental factors able to express their deleterious carcinogenic effect [82, 85].

A protective effect has been attributed to Vitamins C, A, and E as well as diets high in content of fruit and vegetables containing these factors. This is often referred to as a “Mediterranean diet”. There are contradictory results on the effects of garlic consumption, whereas data is overall in favour of a protective effect by long-term consumption of green tea [86].

Overall, it can be stated that a classic Western diet seems to increase the risk for upper gastrointestinal cancers.

Chemoprevention

There is ongoing discussion about the increased cancer risk in patients on long-term PPI treatment, possibly related to the PPI induced hyper-gastrinaemia, which is

also seen in the presence of *H. pylori* [87]. Data is conflicting [88]. There also seems to be no increase in the prevalence of pre-neoplastic changes of the gastric mucosa with long-term PPI treatment from a comprehensive Cochrane analysis in 2014 [89]. Secondary analysis of data from the SOPRAN and LOTUS trial in which some patients were treated with long-term PPI (vs. surgical reflux treatment) did not reveal any difference regarding pre-neoplastic changes of the stomach or neuroendocrine neoplasias within 12 years of follow-up [90]. It has been discussed in the past that although patients on PPI have shown a higher prevalence of gastric cancer in some studies, this result is confounded by the fact that the PPI might have been prescribed for dyspeptic symptoms caused by pre-neoplastic and neoplastic changes in the first place.

Data published in 2018 shows results on a cohort of 63,397 patients from Hong Kong who received long-term PPI after *H. pylori* eradication [91]. PPI intake was associated with an increased risk for gastric cancer (hazard ratio [HR] 2.44; 95% CI 1.42–4.20), which was not seen in patients who received H2RA. The risk further increased with the duration of PPI intake. However, the interpretation of these results requires caution, since a causal relationship cannot be inferred. It must also be considered that patients on PPI were older than non-PPI users (64.1 vs. 54.3 years) and that success of the initial *H. pylori* eradication was never confirmed [91]. Similar results were presented for a nationwide Swedish cohort study including nearly 800,000 patients showing also a threefold risk increased in the standardised incidence ratio (SIR) for gastric cancer among long-term PPI users (SIR 3.38; 95% CI 3.23–3.53), in particular those under the age of 40 years (SIR 22.76; 95% CI 15.94–31.52) [92]. There was no significant difference of this effect regarding cancer location. Patients on additional Aspirin showed a lower risk. Again, there was no risk associated with use of H2RA. It is of note that a subsequent analysis of the Hong Kong data also assessed the impact of combined use of PPI and Aspirin. While long-term PPI intake was associated with an increased risk of gastric cancer among non-Aspirin users (HR 3.73; 95% CI 2.11–6.60), this was not the case for patients taking Aspirin in addition to PPI (HR 0.35; 95% CI 0.04–2.74) [93]. The interaction between these drugs and the implication for cancer prevention require further elucidation. Overall, the current evidence is still inadequate to establish causal relationship, but PPI should only be used for the correct indication and at the lowest effective dose [94]. Long-term treatment or inappropriate dose escalation in non-responders should be avoided.

As indicated above, intake of Aspirin and NSAIDs is suggested to have a protective effect due to reduction of the chronic inflammatory activity in the gastric mucosa [95]. However, evidence is not strong enough to give a general recommendation for intake of these compounds with the aim of cancer prevention, particularly in the view of an increased risk for gastro-duodenal ulcers as well as beneficial impact on the cardiovascular system. Most consistent was the effect for intake of Aspirin as shown in an analysis on 650,000 patients who took Aspirin for longer than 10 years resulting in a risk reduction of nearly 50% [96]. Regular intake of Aspirin had to be maintained and the effect could not be confirmed for other NSAIDs as also reported in other studies [97, 98]. Data on the benefits of COX-2 inhibitors is conflicting but show signs for improvement of pre-neoplastic conditions like chronic atrophic gastritis and gastric IM [99, 100]. Comparison of these studies is often quite difficult due to heterogeneous design, differing end-points and variation of inclusion and exclusion criteria.

Similar to the data presented above for OAC, several observational and case-control studies have demonstrated a protective effect of statins regarding the risk for gastric cancer development. Most studies show a risk reduction in a range of 30–40% [101–103]. However, it is not clear if there is a dose-dependent effect, also regarding the duration of treatment.

H. pylori Eradication

Infection with *H. pylori* is the most relevant risk factor for gastric cancer. The Kyoto consensus has recently defined *H. pylori* gastritis as an infectious disease that has to be eradicated when diagnosed [104]. The first meta-analysis that confirmed a preventive effect from eradication of *H. pylori* was published by Fuccio et al. [105] in 2009, stating a reduction of gastric cancer incidence by 35% analysing data from 6,695 patients. A population-based study from Taiwan including more than 4,000 individuals in which 78.2% of *H. pylori* could be eradicated confirmed a risk reduction for gastric cancer of about 25% [106]. Despite these positive findings, the actual effect was lower than anticipated. Thus, *H. pylori* eradication alone does not necessarily abolish gastric cancer risk. A prospective, randomised, double-blinded placebo-controlled eradication trial from China followed 1,630 patients for 7.5 years after intervention [107]. The primary endpoint of this study was missed with no statistically significant difference in gastric cancer incidence between the study arms. However, secondary analysis showed that adenocarcinoma only developed in patients who present-

ed with pre-neoplastic changes (atrophy and/or IM) at study inclusion. When adjusted for these findings, the effect of *H. pylori* eradication was highly significant. So, patients with pre-neoplastic conditions at the time of eradication carry further the risk for gastric cancer development and this risk is associated with the degree and distribution of the respective changes [108–112].

There is great interest in the definition of the “point of no return” from which point, eradication treatment will not prevent further progression of pre-neoplastic changes. A nationwide cohort from the Netherlands demonstrated follow-up data over 5 years for more than 90,000 patients reporting a stepwise increase of the annual gastric cancer incidence from 0.1% in patients with chronic atrophic gastritis, to 0.25% in patients with IM, 0.6% in those with LGD and 6% in patients with HGD at index endoscopy [113]. Similarly, an observational cohort of 405,172 individuals in Sweden showed an incidence of gastric cancer in 1 out of 256 patients with initially normal mucosa, 1 out of 85 patients with gastritis, 1 out of 50 with atrophic gastritis, 1 out of 39 with IM and 1 out of 19 with dysplasia [114]. According to results from meta-analyses, eradication treatment can induce regression of atrophic changes of the gastric mucosa but has no impact on IM [115, 116], which is the reason for the presence of IM being currently considered to mark the “point of no return” [117]. Age alone should not be the rationale to decide if eradication is indicated. Older patients can still benefit from successful treatment of the infection. A recent analysis from Hong Kong showed a particular benefit of *H. pylori* treatment for patients of 60 years of age and older [118].

Although the eradication of *H. pylori* might not abolish gastric cancer risk in patients with advanced mucosal alterations, it might still confer a beneficial protective effect. Fukase et al. [119] reported a reduction of meta-chronous neoplasia by *H. pylori* eradication after endoscopic resection of early gastric cancer. This had been confirmed in a 2016 meta-analysis of 10 studies including 5,881 patients reporting a risk reduction of more than 60% (OR 0.39; 95% CI 0.259–0.593; $p < 0.001$) [120]. And final clarity on this issue was given by a recently published prospective double-blind, placebo-controlled randomised trial on 470 patients undergoing endoscopic resection of early gastric cancer or HGD [121]. Median follow-up time was 5.9 years with meta-chronous lesions occurring in 14 patients (7.2%) in the treatment group and 27 (13.4%) in the placebo group. This demonstrated a 50% risk reduction by eradication treatment (HR 0.50; 95% CI 0.26–0.94, $p = 0.03$) [121].

Knowledge of further relevant factors that influence the effect of *H. pylori* eradication is expected from the interventional study that is currently being undertaken in the Chinese province of Linqu with international support [122]. The 185,000 inhabitants of this region were tested for *H. pylori*, and then randomised as to whether they received eradication prior to long-term follow-up. The study aims to demonstrate the feasibility of population-based mass eradication and potential influencing factors. As indicated above, data from Taiwan already indicated the benefits of mass eradication in high incidence areas [123].

The best option for “global eradication” would be given by an *H. pylori* vaccine. A suitable vaccine is yet to be developed. A Chinese prospective, double-blind, placebo-controlled phase III study in children aged 6–15 years demonstrated a preventive effect in 70.8% by an oral recombinant vaccine [124]. These data remains to be confirmed and further discussion is warranted if *H. pylori* should be eradicated at such an early age. Data from another study testing an intramuscular vaccine in young healthy adult volunteers did not show adequate protection against the infection in this group. But interestingly, an enhanced immune reaction was seen in participants who received the vaccine (compared to placebo) [125]. All study participants were challenged with inoculation of a CagA positive *H. pylori* strain and it was interesting that the adult immune system proved to be quite competent to repel this infection with more than half of the subjects in the placebo arm failed to establish the infection.

Secondary Prevention

Secondary prevention of gastric cancer focuses on early detection of the disease when minimally invasive treatment can be offered with curative intention. Endoscopic surveillance of patients even after eradication of *H. pylori* is associated with the detection of early stage cancer and therefore better outcome [126]. A recent review by Rugge et al. [164] delivers a comprehensive overview on this topic. As outlined above, patients with IM and atrophic changes require regular endoscopic assessment because they have particular risk of progression towards cancer. The risk is increased three- to fivefold when atrophy and/or IM is extensive [107, 127]. Extent and distribution of the mucosal alterations further influence the risk [114, 128–130]. The annual progression rate of advanced pre-neoplastic lesions is – similar to data from BO – around 0.3% [131]. Biopsies for the assessment of the gastric mucosa should be taken and histopathologically assessed ac-

cording to the updated Sydney classification [132]. Further stratification into the more recently developed Operative Link for Gastritis Assessment (OLGA) or Operative Link for Gastritis Assessment by IM systems allow even more precise individual risk assessment [133–135]. Although Operative Link for Gastritis Assessment by IM shows a favourable interobserver variability, data for OLGA is more comprehensive and it has been suggested that a combination of both approaches be used [136–139]. Rugge et al. [140] recently presented data on 7,436 patients who were followed-up for a median of 6.6 years. At index endoscopy, 97.7% of the patients presented in OLGA stages 0, I, and II, whereas only 2.3% showed high risk stages III and IV. And although there were 6 cases of incident gastric cancer in OLGA low risk patients, the majority of lesions developed in stages III and IV with these stages being confirmed as independent risk factors in multivariate analysis. The HR for OLGA III was as high as 712.4 (95% CI 92.54–5,484.5) and for OLGA stage IV even higher (HR 1,450.7; 95% CI 166.7–12,626.0) [140].

European guidelines recommend endoscopic surveillance every 3 years in case of advanced atrophy (or IM) [128]. Surveillance cannot be recommended in case of focal atrophy or IM, since the low progression rates (<1.8% even after 10 years) result in inadequate cost-effectiveness ratios [113, 141]. In addition to “random” biopsies according to the updated Sydney protocol, also targeted samples from visible lesions should be taken to increase the diagnostic yield [142]. Although the strategy of 3-yearly endoscopic surveillance seems to be successful and cost effective also in a European setting, further prospective studies are required to deliver definite proof of its benefit [143–145]. The main issue remains the primary identification of patients who should undergo endoscopic surveillance. While population-based gastric cancer screening is established in Japan, Korea and Taiwan, this cannot be recommended for low incidence Western countries. Attempts are being made to improve the strategy by stricter selection criteria for patients undergoing surveillance [146] and by machine learning-based computational approaches for the assessment of endoscopic images, which might decrease the number of necessary biopsy samples [147].

Serological Pre-Screening

Serological pre-screening of individuals to identify those with the high likelihood for presence of pre-neoplastic conditions has since long been set in practice in Japan and more recently also in Korea. The best investi-

gated surrogate marker is serum pepsinogen I and the pepsinogen/II-ratio. Watabe et al. [148] showed in a study of 9,293 Japanese subjects that the combination serum pepsinogen assessment and testing for anti-*H. pylori* antibodies was highly predictive for the development of gastric cancer [148]. Similar results were achieved in a study that considered only serum PG values and did not include *H. pylori* serology in the analysis [149, 150]. A meta-analysis confirmed a risk-increase of gastric cancer by factor of 6 to 60 in cases with a pathological PG test and positive *H. pylori* serology [151]. Patients with positive test results should then undergo endoscopic assessment, a strategy that has been demonstrated to be effective in a Japanese meta-analysis of 40 studies with more than 300,000 participants [152]. The application of this strategy in certain regions in Asia led to a reduction of gastric cancer-related mortality by 76% [153].

A meta-analysis including data from European studies indicates similar results, although study heterogeneity does not allow to draw valid conclusions [154]. However, several cohort studies with follow-up up to 14 years showed promising results [149, 155–157]. Although serum PG assessment shows good diagnostic properties for the detection of gastric mucosal atrophy (sensitivity 74.4%, 95% CI 62.0–84.3; specificity 95.6%, 95% CI in 92.6–97.4) in a recent meta-analysis, this strategy cannot yet be recommended for countries with low incidence of gastric cancer [158]. Pre-selection of certain risk groups like smokers might be necessary to result in adequate protection against mortality from intestinal type gastric cancer and increase its cost effectiveness [159].

Similarly, a population-based “screen-and-treat” for *H. pylori* infection is currently not recommended for most regions in Europe [159]. Cost effectiveness could be

improved if these tests are coupled with colorectal cancer screening, which has already been implemented in most European countries [160–162].

Summary and Conclusion

Prevention of OAC focuses on endoscopic surveillance of BO for detection of early dysplastic/neoplastic lesions, which are treatable by endoscopic modalities. Surveillance intervals depend on the macroscopic (e.g., length of the segment) and microscopic (e.g., presence and degree of dysplasia) characteristics of the meta-plastic segment. New methods for minimally invasive Barrett’s detection are promising but still require validation of the merit in clinical routine settings. In the primary prevention of gastric cancer, the eradication of *H. pylori* infection remains the most powerful intervention. It cannot be emphasized enough that confirmation of successful eradication is a crucial part of any attempt to treat this disease. Better understanding of the biology of gastric pre-neoplastic lesions will allow a precise definition of the “point of no return” when eradication is no longer effective in halting the progression towards gastric neoplasia and thus selection of those patients who require endoscopic screening in regular intervals is required [104, 163]. Future research will have to elaborate on simple methods for pre-selection of patients at high risk to allow their implementation in strategies and respect all demand of cost effectiveness.

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There are no conflicts of interest for the authors regarding the contents of this article.

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