Current views

Is there any relationship between esophageal adenocarcinoma and anti-reflux surgery?

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SUMMARY

Esophageal adenocarcinoma presents a more rapidly rising incidence than all other cancers and arises in most patients from its premalignant precursor, Barrett's esophagus. Barret's esophagus is associated with chronic GERD and represents the severest form of this disease. PPIs can markedly decrease acid reflux, but only antireflux surgery can successfully restore the function of the incompetent antireflux barrier. Antireflux surgery may be superior to controlling acid reflux alone, because it also eliminates the possible dangerous contributions of bile salts and pancreatic enzymes. However, current data suggest that both medical and surgical therapies are very effective in symptom relief and healing of esophagitis over the long term, but neither treatment predictably causes Barrett's metaplasia to regress, nor protects the patient from subsequently developing adenocarcinoma of the esophagus. Even if antireflux surgery could prevent esophageal cancer, its use only for this purpose could not be justified because the surgical mortality rate, at least 0,2%, far exceeds the annual incidence of cancer, estimated at 0,07%. Therefore, it seems prudent for gastroenterologists and surgeons to be honest with their patients about the outcomes of current established treatments of GERD. Given this information, and after a thoughtful discussion of both therapies, we believe patients can choose the regimen that best suits their individual needs.

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ESOPHAGEAL ADENOCA (EA), BARRETT'S ESOPHAGUS (BE) AND GERD

It is well known that over the last three decades, there has been such a dramatic increase in the incidence of EA, of a percentage exceeding 350%,[1] so as to be considered today the malignancy with the most rapidly rising incidence. The cause of this increase remains unclear. The only recognized risk factor for the development of EA is the presence of short or long Barrett's epithelium,[2] a condition that, beyond any doubt, complicates long-standing, severe GERD. Some epidemiological studies suggest that the frequency, duration and intensity of reflux symptoms are risk factors for the development of EA.[3] Even though some other studies indicate that EA may be related to obesity, smoking and to a diet low in fresh fruit, these assumptions seem to be controversial.[4-7] Moreover, the effect of Helicobacter pylori infection, especially of cagA (+) strains, remains in many ways unidentified, although, in the beginning, it had been suggested that it could have a protective role against the EA[8,9]. Therefore, based on the existing data, GERD and especially this one which is complicated with BE, is considered the main risk factor for the development of EA.

Currently, the therapeutic management of GERD involves either conservative treatment with antisecretory drugs or antireflux surgery. The aim of the conservative therapy is to suppress the acid secretion, in an effort to minimize the deleterious effects of acid on esophageal mucosa. On the other hand surgical management restores the incompetent antireflux barrier. Moreover, the application of a laparoscopic approach in the performance

of antireflux surgical procedures, which means less postoperative pain, lower morbidity, quicker recovery and return to daily activities, similar functional results and lower overall cost in comparison to the open surgical procedure,[10,11] has contributed to the wide application of the surgical management of many patients.

THEORETICAL ADVANTAGES OF ANTIREFLUX SURGERY

The main theoretical advantage of surgical management is that it also controls the reflux of duodenal contents, which are rich in bile salts and pancreatic secretions. It is known that patients with only gastric reflux develop less damage to the esophageal mucosa, compared to those with mixed gastric and duodenal reflux, as acid and bile salts can act synergistically for the development of EA and induce carcinogenesis.[12-14] Duodenal contents, rich in pepsin, bile salts and lysolecithine can cause damage to esophageal mucosa in the following ways:

- Pepsin increases the sensitivity of esophageal mucosa to acidic reflux, as smaller acid concentrations (pH 1,6-2) are needed to induce damage. On the other hand, esophageal mucosa is outstandingly resistant to pure acid reflux, as great quantities of acid are needed to cause similar damage (pH 1-1,3).
- Conjugated bile salts are more noxious in pH<3 but inhibit the damaging effect of pepsin in an acidic environment, than unconjugated bile salts in pH 5-8.
- Lysolecithine causes damage when HCl is present, while its absence has no effect.
- Trypsin is inactivated in pH<4, while its damaging effect is exhibited in pH>7 and is enhanced by the presence of unconjugated bile salts.

From these data it can be concluded that there is a synergistic action between HCl and pepsin, HCl, conjugated bile salts and lysolecithine, and unconjugated bile salts and trypsin[14]. Therefore, it seems that when HCl is absent, there is no damaging effect of any of the above mentioned factors, with the possible exception of trypsin and unconjugated bile salts. However, the latter may be more detrimental, as they can promote cell mutations, and, under some circumstances, act as cancerogenic[15]. *In any case, it is generally accepted that the presence of basic esophageal pH (>4) inhibits even the most noxious effects of duodenal contents, and this can be achieved in the majority of patients with aggressive antisecretory treatment.*

Additionally, recent data show that mixed acidic and duodenal reflux has more complex effects on the cell differentiation and proliferation of Barrett's epithelium. Prolonged acid exposure increases cell differentiation but blocks cell proliferation, while pulses of acid enhance cell proliferation without altering cell differentiation. Similarly, pulses of bile salts enhance proliferation, but this effect is blocked by the addition of acid.[16] Furthermore, pulses of acid or bile salts significantly increase COX-2 expression in BE and EA.[17] It is known that COX-2 functions as a rate-limiting enzyme in the generation of prostanoids from arachidonic acid, and its overexpression may be mutagenic and tumourigenic.[18] In fact, overexpression of COX-2 promotes proliferation, inflammation and esophageal mucosal thickening, probably through a complex kinase activation cascade, and in this procedure bile salts seem to have the leading role.[19] The aforementioned findings show that mixed acidic and duodenal reflux promotes the cell proliferation of Barrett's metaplastic epithelium, which can lead to EA. Therefore, it seems reasonable to assume that prevention of mixed reflux could normalize cell proliferation of metaplastic epithelium and probably decrease the risk of esophageal cancer.

A very recent study[20] has provided significant information about the progression of BE to dysplasia and EA. It suggests that gastrin increases cell proliferation of metaplastic epithelium and therefore may act as a mutagenic and tumourigenic in patients with BE. This conclusion is of great significance, because patients who are treated with PPIs, may have secondary hypergastrinemia, and, if the above assumption is valid, they theoretically have an increased risk of EA.

We should also keep in mind that some patients who are treated conservatively with full dose of PPIs do not seem to respond adequately, for unidentified reasons. In another recent study, it was demonstrated that in patients with BE, who were receiving full dose of PPIs, GERD was not effectively controlled, and there was enhanced cell proliferation and decreased cell differentiation in their biopsy specimens, in contrast to those in whom acidic reflux was effectively controlled.[21] This observation is in agreement with previous studies, which showed that in a subgroup of patients, administration of full dose of PPIs may not be adequate and addition of ranitidine should be considered in order to avoid nocturnal "acid breakthrough".[22]

Moreover, in some studies, it seems that surgical treatment can result in partial[23] or even complete[24] regression of BE, or eliminate low-grade dysplasia in Barrett's metaplastic epithelium,[25] thus decreasing the

risk of developing EA. However, most authors agree that complete regression of BE is at least uncommon and may well represent "pseudoregression" due to surgical repositioning of the esophagus.[26] Furthermore, other studies[27,28] have shown that either dysplasia or cancer can develop in patients with BE who undergo antireflux surgery. Finally, partial regression of Barrett's esophagus has been documented, either after aggressive antisecretory treatment[29] or after surgical treatment, if it is followed by treatment with PPIs.[30,31]

SURGICAL VS MEDICAL TREATMENT OF GERD IN THE PREVENTION OF EA

Currently, 3 studies suggest that antireflux surgery may prevent malignant progression of BE to dysplasia and EA more efficiently than medical treatment. In the first,[32] 59 patients were randomized and 27 of them received therapy with PPIs, while 32 underwent antireflux surgery. The mean follow-up was 4 and 5 years, respectively. Five patients in the conservative group developed dysplasia, whilst none in the surgical group did so. One patient in each group developed EA; however, the patient from the latter group was noted to have a failed antireflux surgery. In the second, the long-term follow-up experience of patients who had undergone antireflux surgery in Mayo Clinic was reported.[33] Three cases of EA were notified in the early follow-up period at 13, 25 and 39 months respectively, and the authors suggested that these three cancers could have been occult at the time of surgery and simply not detected. However, late cancers were not seen despite the long follow-up period of 18,2 years (mean duration 6,5 years). Finally, in a retrospective study[34] of 102 patients with Barrett's esophagus, treated conservatively and followed for a median of 4,8 years, 19 developed new-onset low-grade dysplasia and 4 evolved to high-grade dysplasia with 3 progressing to adenocarcinoma. On the other hand, none of the 15 patients who underwent antireflux surgery developed dysplasia or adenocarcinoma.

The above studies, even though they have methodological defects, compare the efficacy of surgical versus conservative treatment in the prevention of EA and they all give the advantage to the surgical approach. However, the subsequent data of the first study[32] are reported in a most recent publication[35] and present different results. 101 patients with short or long Barrett's epithelium were included, of whom 43 were medically treated (median follow-up: 5 years, range 1-18 years), while 58 were surgically treated (median follow-up: 6 years, range 1-18 years). 2 patients from each group eventually developed high-grade dysplasia (5% vs 3%), and all of them were included in the group of patients in whom GERD was not effectively controlled, as was proved by 24h ambulatory pH monitoring. *Therefore, the conclusion is that the risk of progression to EA is significantly decreased when GERD is effectively controlled either medically or surgically.*

Moreover, in 3 other studies, similar results were shown. In the first one,[36] 37 patients with BE after antireflux surgery were compared to 140 patients on conservative therapy. Four patients in the surgical group developed mild dysplasia and 2 of them progressed to high-grade dysplasia, while one patient developed EA without first developing dysplasia. The incidence of EA in the surgical group was 1 in 48 patient years, compared to 1 in 99 patient years for the entire study population. In the second prospective study[37] it was found that 4 patients (2%) in the medical group and 1 patient (1,2%) in the surgical group developed EA after a mean follow-up of 7,1 years (range 4-12 years). Of these 5 patients, 4 had previously documented BE and there were no statistically significant differences between the two groups.

Finally, in another well-designed, large, retrospective study[38] which included all the patients who underwent antireflux surgery in Sweden, over the last 32 years as well as all EA reported to the National Cancer Institute, it was demonstrated that the incidence of EA was 6-fold higher in patients treated conservatively, compared to the general population, while it was 14-fold higher in patients treated surgically.

CONCLUSIONS

GERD and Barrett's esophagus are the principal risk factors for the development of EA and, currently, the best way to prevent it is the effective treatment of GERD. *Both surgical and medical therapies are equally effective, at least in the majority of patients.*[39] In some cases however, even when the disease is completely controlled, the risk of EA still exists. The reason remains to be elucidated and certainly more studies are required, especially studies concerning the pathogenesis of EA.

Even though current data suggest that the various types of antireflux surgery do not outweigh the classic aggressive antisecretory treatment in the prevention of EA, even if that was valid, it should not be the "gold standard" since *the surgical mortality rate reaches 0,2%,*[40] *which far exceeds the annual incidence of EA estimated at 0,07%.*[37]

Even in the case of BE, where the annual incidence of EA is about 0,5%,[41] which some enthusiasts suggest should be a definite indication for antireflux surgery, some epidemiological data should be considered; well-documented risk factors for the development of BE in patients with GERD are the presence of large (> 3 cm) hiatal hernia, the duodeno-gastro-esophageal reflux, the decreased resting pressure of the lower esophageal sphincter, and decreased esophageal catharsis.[42] On the contrary, risk factors for the development of EA in patients with BE are the gender (male), the race (white), the age (>50years) and the duration (>5 years) of reflux symptoms[43]. *From these simple epidemiological data we conclude that factors associated with the severity of GERD may account for the development of Barrett's esophagus, while for the progression of Barrett's esophagus to EA, genetic factors seem to play the leading role.*

The deeper understanding of the pathogenesis of the disease may lead us to different therapeutic manipulations. The first trials of chemoprevention with COX-2 inhibitors combined with potent antisecretory therapy have already been published as preliminary studies with promising results.[44] Until efficient data support this hypothesis, *based on the fact that neither the conservative nor the surgical treatment of GERD is better than the other*, the selection of therapeutic manipulation should be individualized. Gastroenterologists and surgeons should be honest with their patients and after a thoughtful discussion of both therapies, the patient himself can choose the regimen that best suits his individual needs.

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