Argon plasma coagulation therapy for ablation of Barrett’s oesophagus

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Endoscopic thermoablation with argon plasma coagulation (APC) for Barrett’s oesophagus is most effective for shorter segments but “buried” glands do occur. APC should remain in the area of experimental clinical studies

Barrett’s oesophagus (BO) is undoubtedly associated with an increased risk of adenocarcinoma of the oesophagus. Now that therapeutic endoscopy techniques have improved, it is therefore tempting to ablate Barrett’s intestinal metaplasia in order to decrease the risk of tumour development. However, ablation therapy is still controversial, especially for patients having no dysplasia, due to: (1) their low risk of cancer; (2) the risk associated with the technique of ablation; and (3) the fact that we do not know if Barrett’s ablation will really decrease the risk of cancer in the long term in an individual patient.

The rationale for current ablative therapy began with the observation that destruction or ablation of intestinal metaplasia associated with acid suppression results in its rapid replacement by a squamous epithelium. Several groups of investigators have performed clinical studies evaluating the effectiveness of BO ablation associated with proton pump inhibitor (PPI) treatment. For patients having non-dysplastic BO without dysplasia, argon plasma coagulation (APC) has been the most popular technique. After 1–6 sessions, a success rate of BO eradication ranging from 42% to 98% was achieved. Chest pain was very frequent after treatment and other complications were unusual, although not negligible since they included strictures, fever, bleeding, or even perforation and death. More importantly for the long term usefulness of this therapy was the observation of persisting buried intestinal metaplasia under the squamous re-epithelialisation, which was observed in the first clinical trials with a frequency of 8–30%. Also, at least two cases of adenocarcinoma arising under the squamous re-epithelialisation have been observed after APC, suggesting that even surveillance (and biopsy targeting) could become more difficult after this therapy. More recent trials have observed a very low incidence of buried glands, probably because of the use of higher PPI doses and of higher power settings of the APC resulting in a deeper injury, but also at the cost of a higher incidence of strictures. In the current issue of Gut, Basu and colleagues report on a series of 50 patients with BO treated by APC and followed for one year [see page 776]. They used a 30 watt power setting of APC (which corresponds to the low range of energy) and cleared the BO macroscopically in 68% of cases, but 44% of those successful cases had buried glands at histology. As reported in other studies, they found that the length of BO was a predictive factor for persistence after treatment. There was a slight trend for persistent acid reflux in cases where eradication was not achieved but this was difficult to evaluate as PPI doses were adjusted to reach effective acid suppression. At one year, they observed a higher rate of BO recurrence in patients who had reduced their PPI use, suggesting that, if eradication is obtained, it should be followed by lifelong high dose PPI therapy to avoid recurrence.

An interesting finding of this paper was the trend towards more severe biliary reflux among patients with persistent BO at the end of treatment, suggesting that acid reflux is not the only factor to be considered when examining the mechanisms affecting outcome of such therapy. Unfortunately, the authors did not perform bilimetry in all patients and may have compromised their chance of reaching a significant difference in this evaluation of biliary reflux and characterising the “factors determining persistence and recurrence of BO”.

Another major concern of such ablative therapy is cost effectiveness. Even if it was successful in every patient, the cost of a median of three endoscopic therapy sessions is not negligible. To that end, however, ablation therapy is still controversial and not applicable for non-dysplastic BO. The study of Basu et al stresses that ablation of non-dysplastic BO is far from being proved useful for patients and should strictly remain in the area of experimental clinical studies.

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Appendicectomy has a protective effect in Crohn’s disease and ulcerative colitis, and the course of ulcerative colitis seems milder following a history of appendicectomy

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Appendicectomy has a protective effect in Crohn’s disease and ulcerative colitis, and the course of ulcerative colitis seems milder following a history of appendicectomy

The endless “genetics or environment” debate can get rather convoluted, whether about inflammatory bowel disease (IBD) or any other complex disease. With regard to IBD, a series of epidemiological and genetic “breakthroughs” have barely inched us closer to clarifying this issue. Indeed, many decades of research on Crohn’s disease and ulcerative colitis have so far revealed just one principal gene, at the NOD2 locus on chromosome 16, and one major environmental factor, smoking, in influencing susceptibility to either of these conditions.

Currently, the “Crohn’s disease gene” is the hottest topic but environmental issues keep pushing themselves into the picture. A protective effect of smoking in ulcerative colitis have so far revealed just one principal gene, at the NOD2 locus on chromosome 16, and one major environmental factor, smoking, in influencing susceptibility to either of these conditions.

Now a newer factor, the role of the microbiome as a severity measure; but overall both papers are consistent with each other as well as with previous studies, and they undoubtedly offer tantalising clues to the pathogenesis of IBD. But Tantalus never did get to eat or drink the food and water surrounding him, and it seems we too are going to have to wait a lot longer before satisfying our own hunger and thirst for understanding everything about IBD.

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Cancer

Risk of pancreatic ductal adenocarcinoma in chronic pancreatitis

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Patients with chronic pancreatitis have a markedly increased risk of pancreatic cancer compared with the general population

Chronic pancreatitis has been proposed as an independent risk factor for the development of pancreatic cancer in a number of important studies. Problems with methodology however, such as patient selection, ascertainment bias, small patient numbers, and stringency of patient selection have been major criticisms, leading some authors to believe that the risk of pancreatic cancer in chronic pancreatitis is confounded by other risk factors such as smoking. The study presented by Malka and colleagues in this issue of Gut has addressed some of these considerations, in that it has prospectively followed a cohort of 373 patients with proven chronic pancreatitis, defined by stringent criteria, over a median of 9.2 years and 60% had diabetes mellitus (54%), pseudocysts (46%), and venous occlusive disease (21%) leave little room for doubt that this is a true cohort of patients with chronic pancreatitis. Patients with pancreatic cancer were confirmed histologically in all cases and careful consideration was given to patients that were lost to follow up. The results of the study suggest a significantly overall increased risk of pancreatic cancer (standardised incidence ratio 26.7) in chronic pancreatitis.

The majority of patients in this study had alcoholic pancreatitis (85%); patients with chronic pancreatitis however are a heterogeneous group, with chronic pancreatitis of other aetiologies having a much greater risk for the development of pancreatic cancer. Hereditary pancreatitis, the risk of developing pancreatic cancer in chronic pancreatitis is also related to the age of the patient. Whether this is a reflection of the age per se or the duration of chronic pancreatitis is unclear. Lowenfels et al, in a study of 1552 patients with chronic pancreatitis, found a marked independent increase in pancreatic cancer with age such that the relative risk for the development of pancreatic cancer was more than three times greater for a patient over the age of 60 years compared with younger patients. In a similar study in patients with hereditary pancreatitis, the risk of pancreatic cancer was negligible below the age of 40 years but increased greatly with age such that the overall lifetime risk to aged 70 was 40%. Cigarette consumption is an important consideration in any study evaluating cancer risk, particularly in chronic pancreatitis where a high proportion of patients smoke. A number of studies have identified smoking as an independent variable in the development of pancreatic cancer, and demonstrated that there is a relationship to the number of cigarettes consumed. In a multivariate analysis of 497 patients with hereditary pancreatitis, smoking was found to independently double the risk of pancreatic cancer and accounted for approximately 10% of all pancreatic tumours. Pancreatic cancer also developed some 20 years earlier in smokers compared with non-smokers, suggesting that smoking compounds the risk of pancreatic cancer in chronic pancreatitis.

Leaving epidemiological studies aside, there is some biological evidence supporting the development of chronic pancreatitis to pancreatic ductal adenocarcinoma. Ductal dysplasia, which is relatively common in chronic pancreatitis, has been demonstrated in the pancreas of patients with pancreatic cancer. More importantly, there is a stepwise progression from mild to severe dysplasia within the pancreatic ducts suggesting a temporal relationship of these ductal lesions and pancreatic cancer. Molecular analysis of pancreatic ductal lesions, similar to those found in chronic pancreatitis, has demonstrated identical molecular lesions as those found in infiltrating ductal adenocarcinomas of the pancreas. K-ras mutations have been described in ductal lesions with minimal atypia and as such are “early” genetic events in carcinogenesis. Mutations in the p16 gene occur at a later stage in carcinogenesis. Yamano et al showed loss of heterogeneity of the p16 loci in 13% of histologically low grade pancreatic ductal lesions compared with 90% of high grade lesions. Loss of expression of p16, another tumour suppressor gene thought to be important in the development of pancreatic cancer, was found in 60/126 microdissected intraductal lesions. More significantly, loss of expression of p16 was seen in atypical lesions three times more often than non-atypical lesions, suggesting that loss of p16 expression occurs more frequently in higher grade duct lesions. Loss of expression of p16 and another tumour suppressor gene SMAD4 have also been seen in pancreatic ductal lesions, but unlike K-ras and p16, these mutations...
are seen in lesions with significant atypia or carcinoma in situ. A direct link may lie in the chronic activation of trypsinogen and activation by trypsin of the matrix metalloproteinase matrilysin (MMP-7), increased activity of which is now recognised as one of the earliest events in the molecular pathogenesis of pancreatic cancer.

Further confirmation of chronic pancreatitis as a risk factor for pancreatic cancer is important from a clinical prospective, particularly with respect to screening. It is clear that unstructured screening of all patients with chronic pancreatitis is unlikely to be of benefit as existing tests are not sufficiently sensitive or specific to result in patients with cancer being detected with the required positive and negative predictive values to enable screening to be effective. It is apparent however that there are subsets of patients with chronic pancreatitis where their individual risk of pancreatic cancer may be sufficiently high to justify screening. Given also that there appears to be a progression of molecular mutations in patients with developing pancreatic cancer, screening using a combination of imaging and molecular tests may be justified in older (>40–50 years) patients with the non-inherited as well as the inherited forms of chronic pancreatitis.

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