OPINION

The future developments in upper GI cancer

Hugh Barr,¹ Max Almond²

¹Department of Surgery,
Gloucestershire Royal Hospital,
Gloucester, UK

²Department of Surgery,
Biophotonics Research Unit,
Gloucester, UK

Correspondence to

Professor Hugh Barr, Department
of Surgery, Gloucestershire Royal
Hospital, Gloucestershire Royal
Hospital, Great Western Road,
Gloucester, GL1 3NN, UK;
hugh.barr@glos.nhs.uk

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Abstract

The ageing population and changes in incidence of upper gastrointestinal cancer will have profound changes for our management of these patients. There is much debate as how to bring forward the diagnosis of early mucosal cancer that may be curable using endoscopy or by surgery. In the older more frail patients, early disease will often be controlled by endoscopic resection and ablation therapy.

Introduction

Mapping of the future with projections up to 2030 in cancer is very important for healthcare resource planning. We anticipate a substantial overall increase predominantly reflecting the expansion of an ageing population.¹ These data do mask some very important trends for those managing upper gastrointestinal cancer. Most notably, it suggests that there will be a continued decline in the incidence of non-cardia gastric cancer in both men and women. This continues the well-documented decline, possibly related to helicobacter eradication. However, this is balanced by the continued rising incidence of oesophageal adenocarcinoma. This is now particularly noticeable in women who appear to be developing the cancer some 10 years after men. The incidence of liver cancer will also rise, but the incidence of pancreatic cancer is likely to remain stable. It is clear that the overall age-standardised incidence rate for cancer has increased in the UK in both sexes from 1984 to 2007, although in the last decade (1998–2007) rates have remained constant. Data on oesophago-gastric cancer from the USA Surveillance Epidemiology and End Results database demonstrate an increased incidence from 3.6 per million in 1973 to 25.6 per million in 2006. However, the rate of annual increase was 8.2% prior to 1996 compared with 1.3% increase in subsequent

years. This apparent slowing in the rate of increase is welcomed but unexplained as yet.²

These future projections are always subject to considerable doubt and variability and must be interpreted with some caution. However, it is important to develop and examine strategies with this data in mind; in particular, we require new initiatives on obesity and smoking. It is now demonstrated that obesity and smoking are risk factors for cancer incidence and have been found to substantially jeopardise treatment outcomes. There is twofold worsening of disease-specific survival, and overall survival after surgery in obese patients.³ Interestingly, alcohol intake, a well-established risk factor for squamous oesophageal cancer, has been shown not to be associated with oesophageal or oesophago-gastric adenocarcinoma with an inverse association with moderate alcohol intake, which clearly requires further study.⁴

Prospects for early detection and intervention to prevent invasive cancer

It is now apparent that current guidelines on the alarm signals of upper gastrointestinal cancer (dysphagia, weight loss, iron-deficiency anaemia, gastrointestinal bleeding, persistent vomiting and abdominal mass) are likely to be appropriate for the detection of advanced cancer. Curative treatment options at this stage may be limited, and there has been little impact on overall survival from these cancers. This has precipitated a very welcome concentration on attempts over the next few years to try to bring forward the diagnosis of dysplasia and early mucosal disease. It appears that routine investigation of patients >55 years with upper abdominal pain rarely detects an early upper gastrointestinal cancer.⁵ Currently, strategies are being explored to try to alert our

population to the problem of persistent, severe and nocturnal heartburn in certain patient groups, and advising an early and high-quality advanced endoscopic examination. This may be a substantial undertaking since it appears that the prevalence of gastro-oesophageal reflux symptoms has increased substantially. Severe and weekly symptomatic reflux has increased over the past two decades by 47%.⁶ These data are of great concern to our patients, the British Society of Gastroenterology and the Association of Upper Gastrointestinal Surgeons. These groups are engaging with our patients and the Department of Health to develop realistic strategies and advice for patients and primary care physicians.

It has to be acknowledged that despite national and international guidelines for endoscopic surveillance of preneoplastic conditions (eg, Barrett's oesophagus) in the upper gastrointestinal tract, adherence is often poor, and surveillance appears to be carried out without conviction of a patient benefit. Improvements have been noted by the use of audits and entry of patients into important clinical trials.^{7,8} In particular, screening for the detection of Barrett's oesophagus, and the subsequent surveillance of those with this condition, have been very controversial issues. Prior to widespread adoption, it must be established that an intervention leads to an improvement in survival and the early detection of cancer. Fortunately, the answer will be established within the next decade within an important randomised control trial. Prescribed protocol surveillance with protocol endoscopic biopsy every 2 years, according to British Society of Gastroenterology guidelines, is being compared with endoscopy at time of need. The trial is Barrett's Oesophagus Surveillance Study, which is fully supported and funded by the National Institute of Health Research (NETSCC Health Technology Assessment 05/12/01) in the UK. It has recruited over 3400 patients, and enrolment was completed 6 months ahead of the scheduled time. This is a tribute to the research networks, and mostly to the tremendous commitment by the UK medical and surgical gastrointestinal community to resolve this controversial issue. The final report is expected by 2021. It is essential that all centres continue with high-quality data submission during the vital follow-up phase.

The UK is leading in other upper gastrointestinal cancer issues, providing high-quality data from properly conducted randomised controlled trials addressing controversial areas. These quality-assured trials are essential, since there is very influential data gleaned from large database studies indicating that the incidence of cancer from Barrett's oesophagus may be less than previously estimated. It is suggested that the annual incidence of cancer is only 0.12–0.13%, or one case per 769 patient-years to one case per 860 patient-years.^{9,10} There is much debate about this data, in particular on the accurate classification and definition of Barrett's oesophagus and hiatal hernia.

It is clear that we must attempt to target those patients with Barrett's oesophagus at greatest risk of progression to cancer. Risk stratification currently depends on the detection of dysplasia. High-grade dysplasia is now an indication for intervention usually with endoscopic therapy, with endoscopic resection and/or radiofrequency ablation. The AIM dysplasia trial has clearly demonstrated that progression to cancer can be prevented by radiofrequency ablation.¹¹ It has been shown that the presence of low-grade dysplasia (LGD) at the time of the diagnosis of Barrett's oesophagus increases the risk of cancer by a factor of 5. These patients are usually advised to undergo increased surveillance and over two-thirds have the diagnosis of cancer within the first year of detection of LGD suggesting that cancer may have been overlooked by the biopsy sampling. The pathological sampling and interpretation has significant inter-observer variation even among expert pathologists, and recently it is reported that LGD has a similar low incidence of oesophageal cancer compared with non-dysplastic disease.^{11,12} The issue of the management of LGD will be resolved within a clinical trial, which is currently being planned.

Risk stratification: genetic susceptibility, prevention and chemoprevention

Familial clustering is evident in patients with Barrett's oesophagus, so it is appropriate to examine genetic susceptibility in addition to lifestyle factors. These data are being collected and analysed within the Chemoprevention of Premalignant Intestinal Neoplasia (ChOPIN) trial incorporating Inherited Predisposition Of Neoplasia analysis of genomic DNA from the Aspirin Esomeprazole Chemoprevention Trial and Barrett's Oesophagus Surveillance Study trials, as part of the Eagle consortium. This is a study of genetic variation across the entire human genome, and is designed to identify genetic associations with Barrett's oesophagus and Barrett's neoplasia. The comparison is of genetic variation in patients with Barrett's versus controls using a dense set of markers across the whole genome. These important data will be available within the next 2–3 years.

Over the next few years, there will be greater understanding of the mechanisms of carcinogenesis in the upper intestine, which will help develop chemoprevention strategies. Currently, the use of proton pump inhibitors to control the symptoms of reflux disease is fairly universal for patients with Barrett's oesophagus. However, the question remains: can they prevent cancer, and what is the dose that should be used? Similarly, aspirin and non-steroidal anti-inflammatory drugs are widely prescribed and used. They have been associated with a reduction in cancer in the gastrointestinal tract.¹³ Again, we expect the Aspirin Esomeprazole Chemoprevention Trial assessing aspirin and esomeprazole on mortality and cancer prevention will report in the next few years. It will provide much needed clarity on risk and benefit.¹⁴

The major problem of gastric cancer is in Japan where the risk of cancer by the age of 75 years is 11%. In the UK, the incidence continues to fall, and the location of the tumour is changing, moving to the cardia. Infection with *Helicobacter pylori* remains the cause of chronic inflammation, metaplasia and gastric atrophy. Screening for *H pylori* antibody and serum pepsinogen as a marker for gastric atrophy may be possible to identify high-risk groups.¹⁵ Currently, and in the future, it is likely that we will concentrate on patients identified at endoscopy with atrophic gastritis, dysplasia and adenomatous polyps. There will be increasing attention to identifying hereditary diffuse gastric cancer with the germline mutations of the CDH1 (E-cadherin) gene. These patients may be offered prophylactic gastrectomy or protocolised endoscopic surveillance. In addition, due to a considerable risk of lobular breast cancer, women with this mutation are recommended mammography and breast MRI from the age of 35 years.¹⁶

Advanced endoscopic imaging with curative endoscopic therapy for dysplasia and mucosal neoplasia in the upper intestine will become more established allowing patients therapeutic options other than radical surgery.¹⁷ In addition, endoscopic resection provides a much better tissue specimen for detailed histopathological diagnosis, in particular to allow differentiation of mucosal from submucosal lesions. These large tissue areas have resulted in an alteration in the diagnosis and staging of mucosal neoplasia in 49% of patients when compared with biopsy sampling.¹⁸ After all visible mucosal lesions (including enhanced imaging endoscopy) have been removed, complete ablation of Barrett's oesophagus is necessary. This is now usually performed with radiofrequency ablation. Comparative trials of other methods of ablation will also proceed, including an examination of thermal and cryo-ablation. Ongoing surveillance will be required for all these patients, and planned clinical trials will allow evidence for the optimal screening interval after complete eradication of the preneoplastic epithelium.

It is important to examine the experience of colleagues in Japan who have adopted a very proactive screening programme for gastric cancer since 1982. They have noted that only 25% of cancers are detected by the established programme. It appears that most early cancers have been found following early consultation by the patients following a heightened awareness within the population, who request endoscopy. Overall, the number of early gastric cancers found has risen from 2% to 63%, and the number treated endoscopically is also rising.¹⁹ Similarly, most patients (>65%) request endoscopy as the first-line examination for the detection of cancer. It appears that opportunistic screening of high-risk groups is the usual practice in other nations with a high incidence of cancer, but there is little high-quality data, and most consider eradication of *H pylori* as important if detected.²⁰

Assessment and treatment of established invasive disease

Surgery with neoadjuvant chemotherapy remains, and is likely to remain the mainstay of definitive therapy for patients with invasive upper gastrointestinal cancer who are considered fit for resection. The chemotherapy and radio-chemotherapy neoadjuvant regimen is likely to change when large clinical trials report soon. The outcomes are improving as multidisciplinary team expertise is concentrated in major resectional centres.²¹ These changes are likely to continue with concentration of expertise for resectional surgery, oncology and advanced endoscopic imaging and therapy. Centres will need to demonstrate audit data supporting the best outcomes. Minimal access surgery will continue to develop with the possibility of sentinel node mapping, vagal sparing resections and modified individualised surgery. The importance of accurate staging is vital to an overall successful outcome. Mucosal neoplasia is best staged using endoscopic resection rather than dependence on endoscopic ultrasound. Lymph node assessment and deeper invasion of the gastrointestinal wall is best done using endoscopic ultrasound with the option of biopsy and fine needle aspiration cytology of suspicious lymph nodes. It is now established within a randomised control trial (Cancer of Oesophagus or Gastricus – New Assessment of Technology of Endosonography: a pragmatic randomised trial-COGNATE) that preoperative endoscopic ultrasound improves survival and generic quality of life.²² The detection of distant metastatic disease is also being improved with positron emission tomography-CT scanning. Overall, the accurate preoperative staging improves surgical outcomes, must be detailed and of high quality. There must also be a detailed review by a multidisciplinary team. The prognostic significance of staging investigations and thus the options offered to patients is undergoing reassessment. The UK is leading this endeavour with a major prospective trial to revise the clinical and molecular stratification of gastro-oesophageal cancer.²³ It is expected that initial data will be available within a few years.

Definitive chemoradiation is frequently used for squamous cell carcinoma of the oesophagus. Increasingly, interesting data is beginning to support its wider use in patients with adenocarcinoma. In some centres, it is being considered as an alternative to the standard therapy of neoadjuvant chemotherapy followed by radical surgical excision.²³ These treatment regimens are well tolerated and the reported outcomes are similar to that of surgical excision. The national portfolio of research into novel therapies for potentially curable upper gastrointestinal cancer, and for advanced disease, is increasing with important ongoing studies. It is vital that all those involved with these diseases actively support these high-quality studies.

The greatest achievement over the past decade is the role of the Research Networks, Specialist Societies and Charities. They have a major commitment through the

National Institute of Health Research to support and conduct peer-reviewed randomised clinical trials. The very considerable investment in these endeavours is bearing much fruit, and is enhancing the evidence base for the management of upper gastrointestinal cancer. We expect to be able to inform our patients, and those burdened with the challenging decisions, on where investment should be placed to obtain maximum benefit for patients.

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References

1. Mistry M, Parkin DM, Ahmad AS, *et al.* (online) Cancer incidence in the United Kingdom: projections to the year 2030. *BJC* 2012 (In Press).
2. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? *Cancer Epidemiol Biomarkers Prev* 2010;19:1468–70.
3. Yoon HH, Lewis MA, Shi Q, *et al.* Prognostic impact of body mass index stratified by smoking status in patients with esophageal adenocarcinoma. *J Clin Oncol* 2011;29:4561–7.
4. Neal D, Freedman ND, Murray LM, *et al.* Alcohol intake and risk of oesophageal adenocarcinoma: a pooled analysis from the BEACON Consortium. *Gut* 2011;60:1029–37.
5. Berrill JW, Turner JK, Hurley JJ, *et al.* Upper gastrointestinal cancer in its early stages is predominantly asymptomatic. *FG* 2012;3:47–51.
6. Ness-Jensen E, Lindam A, Lagergren J, *et al.* Changes in prevalence, incidence and spontaneous loss of gastro-oesophageal reflux symptoms: a prospective population-based cohort study, the HUNT study. *Gut* 2012 (In Press).
7. Bampton PA, Schlothe A, Bull J, *et al.* Improving surveillance for Barrett's oesophagus. *BMJ* 2006;332:1320–3.
8. Jankowski J, Barr H. Improving surveillance for Barrett's oesophagus: AsPECT and BOSS trials provide an evidence base. *BMJ* 2006;332:1512.
9. Hvid-Jensen F, Pedersen L, Drewes AM, *et al.* Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 2011;365:1375–83.
10. Bhat S, Coleman HG, Yousef F, *et al.* Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst* 2011;103:1049–57.
11. Shaheen NJ, Sharma P, Overholt BF, *et al.* Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 2009;360:2277–88.
12. Wani S, Falk GW, Post J, *et al.* Risk factors for progression of low-grade dysplasia in patients with Barrett's esophagus. *Gastroenterology* 2011;141:1179–86, 1186.e1.
13. Rothwell PM, Fowkes FG, Belch JF, *et al.* Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* 2011;377:31–41.
14. Jankowski J, Barr H, deCaestecker J, *et al.* Aspirin in the prevention of cancer. *Lancet* 2011;377:1649–50; author reply 1651–2.
15. Watabe H, Mitsushima T, Yamaji Y, *et al.* Predicting the development of gastric cancer from combining *Helicobacter pylori* antibodies and serum pepsinogen status: a prospective endoscopic cohort study. *Gut* 2005;54:764–8.
16. Fitzgerald RC, Hardwick R, Huntsman D, *et al.* Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. *J Med Genet* 2010;47:436–44.
17. Barr H, Kendall C, Hutchings J, *et al.* Rapid endoscopic identification and destruction of degenerating Barrett's mucosal neoplasia. *Surgeon* 2011;9:119–23.
18. Curvers WL, Bansal A, Sharma P, *et al.* Endoscopic work-up of early Barrett's neoplasia. *Endoscopy* 2008;40:1000–7.
19. Hamashima C, Shibuya D, Yamazaki H, *et al.* The Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol* 2008;38:259–67.
20. Choi KS, Kwak MS, Lee HY, *et al.* Screening for gastric cancer in Korea: population-based preferences for endoscopy versus upper gastrointestinal series. *Cancer Epidemiol Biomarkers Prev* 2009;18:1390–8.
21. The National Oesophago-gastric Audit. Third Annual report. An audit of the care received by people with Oesophago-gastric cancer in England and Wales. London NHS Information Centre, 2010.
22. Russell I, Attwood S, Barr H *et al.* Cancer of oesophagus or gastricus-new assessment of technology of endosonography: findings. *J Epidemiol Community Health* 2010;64:A36–7.
23. Gwynne S, Hurt C, Evans M, *et al.* Definitive chemoradiation for oesophageal cancer—a standard of care in patients with non-metastatic oesophageal cancer. *Clin Oncol (R Coll Radiol)* 2011;23:182–8.