

# Gastric cancer in Europe

## European Union Network of Excellence (EUNE) for Gastric Cancer Steering Group

Correspondence to: W.H. Allum, Department of Surgery, Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ, UK

(e-mail: wmallum@hotmail.com) Published online in Wiley InterScience

(www.bjs.co.uk). DOI: 10.1002/bjs.6197

Gastric cancer is common throughout Europe. In 2000 there were 192 000 new diagnoses, with 158 000 deaths. Outcome has remained poor despite advances in therapy, and an overall 5-year survival rate of about 20 per cent compares very unfavourably with that of 70 per cent achieved in Japan.

European surgeons have tried to emulate the Japanese results. Dutch<sup>1</sup> and UK<sup>2</sup> trials have examined whether extended lymphadenectomy might prove as effective in Western patients. In both trials there was little initial difference between Western D1 dissection and more radical D2 dissection. Prolonged follow-up in the Dutch trial suggests a survival advantage in the D2 group, particularly if splenectomy and pancreatectomy are avoided. In contrast, in a randomized trial an Italian group<sup>3</sup> has produced results similar to those of the Japanese, and reports from Germany<sup>4</sup> and the UK<sup>5</sup> have described similar advantages for D2 lymphadenectomy. Nevertheless, a Cochrane review of extended *versus* limited lymphadenectomy concluded that the former provided no benefit from the evidence available<sup>6</sup>.

There are a number of confounding variables here, including the learning curve for a complex procedure, surgeon and surgical centre experience, and compliance with technical aspects. Although further trials might determine the best procedure for Western patients, these are unlikely to be done. Treatment decisions are now being made on the basis of surgical opinion. The Japanese

rules were developed to standardize surgery so that outcomes could be compared meaningfully within and between institutes. Standardization and audit in Europe are an alternative to ensure that the most effective procedure is available to all patients. A consensus on standards in surgery is, therefore, essential to minimize differences and, by inference, improve outcomes. This would also enable robust comparisons of newer interventions, including minimally invasive procedures and innovative interventional endoscopy.

Non-surgical treatments have been evaluated extensively in well designed trials. The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC)<sup>7</sup>, French cooperative<sup>8</sup> and US Intergroup<sup>9</sup> trials have all shown benefit with perioperative chemotherapy and postoperative chemoradiotherapy. Nevertheless, the 5-year survival rates of 36–45 per cent in these trials are significantly inferior to Japanese results. The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC)<sup>10</sup> has reported a 3-year survival rate of 70 per cent in the control surgery arm compared with 80 per cent in the treatment arm. These trials have confirmed a biological effect with these modalities in gastric cancer, establishing their role in radical treatment. Further studies are required to build on the results. Assessment of biological responses to chemotherapy has shown that not all patients benefit from initial cycles. Early identification and exclusion of non-responders might have advantages.

Those not responding could proceed to surgery rather than undergoing additional non-contributory treatments, whereas responders would proceed with perioperative treatments. Management is thus evolving into an individualized approach, depending on particular characteristics of the patient. A greater understanding of the basic features of tumour biology should extend such tailored concepts.

The role of biological agents, the most appropriate chemotherapy combinations and the place of chemoradiotherapy need to be evaluated in future studies. The sample size for such trials will need to be large if meaningful results are to be achieved. The MAGIC trial took 7 years to recruit 500 patients. Its successor is designed to recruit 1100 patients over 3 years. The Japanese have again set the standard as the ACTS-GC achieved this sample size in 3 years, recruiting from over 100 centres. Future studies must be fully supported and completed in a timely manner. Individual research groups will be unable to complete such studies on their own and funding bodies will be keen to ensure that their resources are used wisely, with worthwhile outcomes likely. Such trials will need multicentre collaboration, almost certainly with an international approach.

The recent increase in oesophago-gastric junctional cancers has been unprecedented in gastrointestinal cancer epidemiology. Siewert and Stein<sup>11</sup> have classified these tumours according to their likely origin. However, there are uncertainties with

regard to pathology and treatment. The current tumour node metastasis staging manual does not include junctional cancers, reflecting a lack of consensus on lymph node spread. This lack of agreement influences differences in approach to lymphadenectomy, and the extent of oesophageal and gastric resection. Non-surgical treatments also vary, with some trials including type II with type III and others type I with type II. The management of junctional cancer, therefore, needs careful evaluation. This would be facilitated by a collaborative approach to collection and audit of evidence from pathological examination, treatment and outcome.

Improving the outcome for patients with gastric cancer must also concentrate on better understanding of tumour biology. The genetics of the disease are complex. Studies of hereditary diffuse gastric cancer implicating E-cadherin germline mutations have enhanced understanding of gastric carcinogenesis; these mutations might influence the sporadic form of the disease. *In vitro* studies have suggested that E-cadherin deregulation is associated with increased expression of the antiapoptotic BCL2, rendering neoplastic cells more resistant to apoptotic stimuli such as taxol. Agents that interfere with BCL2 overexpression in cells with E-cadherin deregulation offer an attractive strategy for novel cancer therapies. Molecular analytical techniques can also identify biomarkers that have greater accuracy for prognosis than conventional systems and can predict response to specific therapies. Translational research is the key to linking basic science with clinical development.

The above considerations imply that significant improvement in the outcome of those with gastric cancer requires collaborative approaches.

Individual institutions and even individual nations have limited resources with which to answer the clinically relevant questions. The International Gastric Cancer Association has established a worldwide forum for the discussion of clinical and basic research. A European Union Network of Excellence (EUNE) for gastric cancer is, therefore, being developed to facilitate clinical and basic research by encouraging European collaboration using the Japanese approach as a benchmark. The aims of the EUNE will be to establish consensus on, and the dissemination of, best practice. It will enhance recruitment into clinical trials, promote translational research, and develop a forum for education and training, including interchange of personnel. In this way it is anticipated that the current inferior results of treatment will become historical and that European patients will in future benefit from outcomes similar to those of their Japanese counterparts.

### Acknowledgements

The EUNE for Gastric Cancer Steering Group comprises W. H. Allum, H.-J. Meyer (Coordinators), A. Garofalo, C. Schuhmacher, G. de Manzoni, M. Degiuli, J. Kulig, C. van de Velde, D. Roukos, H. Barr, W. Nowak, C. Wittekind, A. Sendler, K. Park, H. Hartgrink, J. Haringsma and R. Seruca.

### References

- 1 Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I *et al.*; Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999; **340**: 908–914.
- 2 Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V *et al.* Patient survival after D1 and D2

resections for gastric cancer: long term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer* 1999; **79**: 1522–1530.

- 3 Degiuli M, Sasako M, Ponti A, Calvo F. Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer. *Br J Cancer* 2004; **90**: 1727–1732.

- 4 Siewert JR, Bottcher K, Roder JD, Busch R, Hermanek P, Meyer HJ; German Gastric Carcinoma Study Group. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. *Br J Surg* 1993; **80**: 1015–1018.

- 5 Sue-Ling HM, Johnston D, Martin IG, Dixon MF, Lansdown MR, McMahon MJ *et al.* Gastric cancer: a curable disease in Britain. *BMJ* 1993; **307**: 591–596.

- 6 McCulloch P, Nita ME, Kazi H, Gama Rodrigues J. Extended *versus* limited lymph nodes dissection technique for adenocarcinoma of the stomach. *Cochrane Database Syst Rev* 2003; **(4)CD001964**.

- 7 Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M *et al.* Perioperative chemotherapy *versus* surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11–20.

- 8 Boige V, Pignon J, Saint-Aubert B, Cassier F, Comoy L, Bouchaud C *et al.* A randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLC ACCORD07-FFCD 9703 trial. *J Clin Oncol* 2007; **25**(Suppl): 4510.

- 9 Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN *et al.* Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**: 725–730.

10 Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A *et al.*; ACTS-GC Group. Adjuvant chemotherapy for

gastric cancer with S-1, an oral fluoropyrimidine. *NEngl J Med* 2007; **357**: 1810–1820.

11 Siewert JR, Stein HJ. Classification of

adenocarcinoma of the oesophagogastric junction. *Br J Surg* 1998; **85**: 1457–1459.