



## Meeting report

# The first European Union Network of Excellence for Gastric Cancer conference, Rome, Italy, April 2008

WILLIAM ALLUM, ALFREDO GAROFALO, MAURIZIO DEGIULI, and CHRISTOPH SCHUHMACHER

Department of Surgery, Royal Marsden NHS Foundation Trust, Fulham Road, London, SW3 6JJ, United Kingdom

### Introduction

In April 2008 the European Union Network of Excellence (EUNE) for Gastric Cancer held an international symposium in Rome. There were more than 300 delegates from 14 countries. The program was deliberately designed to allow as much discussion as possible. There was a series of state-of-the-art presentations with an emphasis on highlighting the areas of controversy. In addition there were presentations on current topics under development.

A theme throughout was the need to standardize the approach to gastric cancer diagnosis, management, and treatment in order to facilitate close links between the clinic and the basic science laboratory. There were five main topics: early cancer, treatment of locally advanced gastric cancer, esophago-gastric junctional cancer, multimodal therapy, and quality of life. Each session was summarized by moderators and at the end of the meeting topics were identified for subsequent collaborative work.

This report describes the proceedings of the meeting and is based on the presentations given by the faculty members (Appendix).

### Early gastric cancer (EGC)

*Prognostic and predictive factors: M. Mattolese and A. Scarpa*

The development of gastric cancer is increasingly being recognized as a relationship between host and environmental factors. Mattolese described features of genetic susceptibility which are observed in the development of intestinal-type gastric cancer. Loss of heterozygosity

and somatic mutations of the *APC* gene are observed in 20%–40% of gastric adenomas, 6% of patients with intestinal metaplasia, and more than 50% of intestinal-type gastric cancers. The molecular biology of *Helicobacter* infection and the development of gastric cancer has been established. Progression to neoplasia appears to be a balance between apoptosis and proliferation. The Fas antigen pathway of apoptosis seems to be suppressed with persisting *Helicobacter* infection facilitating the Fas pathway for proliferation. There is differential expression of Fas ligands between intestinal- and diffuse-type cancer, supporting distinct mechanisms of malignant transformation.

The catalogue of gene alterations is growing rapidly. Multiple genetic and epigenetic alterations are involved over the course of the multistep conversion of normal cells to cancer. Identification of specific genetic pathways may predict prognosis and influence treatment selection. Scarpa described data from DNA analysis showing how cases of microsatellite instability have a better prognosis than those with microsatellite stability. In addition, cancers which are positive on immunohistochemistry for the *APC* gene have a better prognosis than those with negative expression. DNA extraction, polymerase chain reaction PCR-RNA extraction, microsatellite assays, and microarray techniques are among the variety of techniques to facilitate this rapidly developing area of knowledge.

*Hereditary gastric cancer: F. Roviello*

The majority of gastric cancers are sporadic. However, there is a small proportion of familial cases. Roviello presented detailed data on hereditary diffuse gastric cancer (HDGC). Following the demonstration of familial aggregates of gastric cancer in a New Zealand Maori family, germline mutations in epithelial cadherin were identified. E-cadherin is responsible for intracellular adhesion. It is considered to suppress invasion, and

deregulation is often seen in advanced cases of sporadic gastric cancer. Underexpression is reflected in infiltration and metastatic potential due to less cellular adhesion. Subsequent studies have characterized HDGC, and the International Gastric Cancer Linkage Consortium (IGCLC) has defined criteria to identify HDGC.

The alteration of E-cadherin in HDGC reflects a “two-hit” phenomenon. Genetic mutation is the first and loss of heterozygosity is the second hit. To date 89 germline mutations have been identified. The IGCLC has recommended that in families with diffuse gastric cancer or families of young patients with sporadic gastric cancer, screening for the *CDH1* gene coding for E-cadherin should be undertaken. Those with germline mutations should be offered prophylactic total gastrectomy or endoscopic surveillance. This must be supported by appropriate careful genetic and clinical counseling. Endoscopic surveillance is complicated, as areas of gastric cancer may be multifocal and chromoendoscopy is the preferred technique.

#### *Diagnosis—endoscopic developments: P. Bhandari*

Although endoscopy is the basic technique for a diagnosis, a significant number of early lesions are missed. Bhandari reported that up to 10% of 200 patients had had a normal endoscopy within 3 years of the diagnosis of an esophago-gastric cancer. The persistent problem of EGC detection is lesion recognition. Endoscopic developments include high-resolution endoscopy, chromoendoscopy, narrow-band imaging, autofluorescence imaging, and confocal endomicroscopy. Assessment of abnormalities with appropriate biopsy should be as comprehensive as possible to minimize sampling error. The Cleveland Clinic protocol stipulates that in Barrett’s esophagus there should be four quadrant biopsies every centimeter and each biopsy should be sampled five times. Despite this approach the endoscopist may sample only 0.3% of the total surface and the pathologist may examine only 5% of the area sampled. There is an opportunity for the European Network to set protocols for endoscopy and histological examination.

Chromoendoscopy with agents such as indigo carmine enhances the identification of flat elevated gastric lesions and, with acetic acid, flat lesions in Barrett’s. Autofluorescence imaging is effective but has significant false-positives. Narrow-band imaging is evolving but looks very promising for the future. However, the endoscopist must be highly skilled and have a good understanding of early neoplasia. This can be aided by developing comprehensive educational tools, such as an atlas of endoscopic abnormalities, to improve lesion recognition.

#### *Barrett’s metaplasia: H. Barr*

The conventional approach to the management of confirmed high-grade dysplasia (HGD) in association with Barrett’s metaplasia is esophageal resection, on the basis that most patients will progress to malignancy or will already have small foci within the area of dysplasia. Barr challenged this approach, citing evidence from studies of photodynamic therapy (PDT) and endoscopic mucosal resection (EMR). In a multicenter study of PDT in HGD, not only was HGD ablated but the rate of progression to cancer was significantly slower. In a separate study the outcome for patients treated by EMR for Tis and T1 esophageal cancer was the same in comparison to a parallel group treated by resection. Barr proposed a paradigm shift from the surgical efficiency of resection to the eradication sufficiency of endoscopic treatments. In many patients control of the process can be achieved by repeated treatments as necessary and as effectively as major surgery without the inherent operative risks. Developing studies are evaluating this further in randomized trials of intervention in HGD and early cancer, and these will inform future approaches.

#### *Treatment: Ha van Quyet, M. Catarci, and T. Sano*

Many centers have limited experience of EGC, largely reflecting a low population disease prevalence. Van Quyet presented experience from Hanoi, Viet Nam, where over a 10-year period 110 patients with EGC were treated surgically. A third of patients required chromoendoscopy for diagnosis and false-negative biopsies were most frequently seen in the depressed lesions. Treatment was by D1 or D2 gastric resection and the overall 5-year survival was 97.1%. Pathologically, node positivity was found in 11.8% and this was most often observed in the depressed or excavated lesions.

Sano presented the current approach in Japan for the treatment of EGC. Although a proportion of EGCs are diagnosed through mass screening, a greater public awareness of the disease means more of the population come forward for examination of minor symptoms. The key issue for the local treatment of EGC is the risk of lymph node metastasis, which is approximately 10% irrespective of the series. In mucosa-only disease 3% have lymph nodes involved and 20% of submucosal cancers are lymph node-positive, with 5% of submucosal cancers extending to the N2 tier. The initial Japanese guidelines recommend EMR for 2 cm or smaller mucosal cancers which are histologically differentiated and not ulcerated.

Endoscopic submucosal dissection (ESD) enables larger lesions to be removed, including those with ulcers,

and the guidelines have been recently extended. Effectively, EMR is a large biopsy using polypectomy techniques to remove as deep as the submucosa, whereas ESD is local surgery and can extend to full-thickness wall excision. In both techniques completeness of pathological excision is essential.

The role of sentinel node biopsy (SNB) requires careful evaluation. Catarci described that validation studies have confirmed the feasibility of SNB with a detection rate of 96% and a sensitivity of 93%. However, false-negative rates are appreciable in T2 and T3 tumors, possibly reflecting more complex lymphatic networks. Also, as in other tumors, the implications for micrometastases need to be determined. Their detection is enhanced by more detailed pathological examination including PCR analysis. However, the effect of micrometastases on outcome and therefore their role in determining the most appropriate treatment remains to be established. Early data suggest that nodes with micrometastasis are associated with a poorer prognosis and would indicate selective approaches to lymphadenectomy.

### Summary

1. Translational research should be fully supported to allow identification of markers of biological activity and prognosis to select patients for radical or less radical treatments.
2. There should be interaction between laboratories concentrating on local expertise and resources.
3. There should be application of the knowledge from developments in hereditary diffuse gastric cancer to understanding of the molecular basis of sporadic cancer.
4. Training in endoscopy should be improved to increase recognition of early and high-risk lesions. An initial simple approach would be to develop an educational multimedia resource of examples of early lesions.
5. Agreed protocols for endoscopic examination, lesion sampling, and pathological examination should be developed.
6. Training in endoscopic mucosal and submucosal resection should be developed within Europe.

### Locally advanced gastric cancer (LAGC)

*Adequate surgery: M. Degiuli and T. Sano*

Locally advanced gastric cancer (LAGC) includes patients with clinical T2-T3, N0-N2, and/or T4, N0-1 cancers. Patients with positive peritoneal cytology washings are included in LAGC but are considered at high risk of early peritoneal recurrence.

A correct definition of adequate surgery needs to include the extent of gastric resection and of lymph node dissection. The debate on “distal-” versus “total-gastrectomy de principe”, developed during the 1980s. Despite the theoretical oncological advantage of total gastrectomy, in practice, the routine use of total resection in distal tumors has no survival advantage compared with partial gastrectomy. Total gastrectomy is required for Borrmann type 4 cancers at any location. In addition, if the tumor is located close to the greater curvature and beyond Demel’s point, a total gastrectomy is necessary, largely because the lymph drainage is into the splenic hilus along the splenic artery. Some authors have recently suggested that in diffuse-type cancers the proximal clearance to the esophago-gastric junction should be increased to 8 cm, and this would indicate total gastrectomy in some cases where a distal resection would have been possible. In intestinal-type the more conventional margin would be preferred.

The approach to cardia and subcardia gastric cancers has been carefully evaluated in the Japan Clinical Oncology Group (JCOG) 9502 trial [1], in which patients were randomly allocated to a trans-hiatal approach or a left thoraco-abdominal approach. The study demonstrated that extended total gastrectomy for these tumors via a trans-hiatal approach had a prolonged survival in comparison with the thoracoabdominal approach, and this may reflect an adverse physiological effect from exploring both the abdomen and the thorax.

The extent of adequate lymph node dissection has been debated extensively. The impressive results reported from Japanese and Far East centers with the routine use of extended and systematic lymph node dissection (at least D2 gastrectomy) failed to convince many western surgeons, as the data were not derived from randomized controlled trials (RCTs). A number of trials have since demonstrated an advantage with extended lymphadenectomy. The Italian Gastric Cancer Study Group trial confirmed the safety of D2 resection in western patients and a better survival for T2/3 and node-positive patients. Recently a long-term survival benefit of the extended procedure has been reported from Taiwan in a well-designed RCT.

The role of more extended surgery has been investigated in the JCOG 9501 trial from Japan, in which the lymph node dissection was extended to include para-aortic nodes. This type of surgery was associated with longer operative time, a larger volume of blood loss, and a longer hospital stay, but with no advantage to long-term survival. Therefore, currently, the D2 gastrectomy represents the gold standard for the treatment of LAGC in appropriate patients.

The definition of a D2 lymph node dissection has also been debated. In anatomical terms it is defined according to the relevant lymph node stations in relation to

the location of the primary tumor. The actual number of nodes is subject to individual variability; therefore, it has been suggested that a D2 dissection should excise a minimum of 25 nodes. The established method of staging nodal disease requires a minimum of 15 nodes according to the TNM 6th edition. There has been recent evidence that the ratio of the number of lymph nodes involved with metastases to the number of removed lymph nodes can be a more accurate prognostic indicator, but this can only be valid if a minimum number is harvested. The important conclusion to this issue is that such surgery should be quality-assured by specific criteria and as a result there should be standards established to record the type of procedure undertaken, with reference to individual node stations and location of the primary tumor. Thus, such surgery should be preferably performed at reference centers working to agreed protocols

#### *R0 resection: D. D'Ugo*

The definition of an R0 resection proposed by Hermanek in 1994 [2] describes a microscopically negative resection margin with no microscopic tumor remaining in the tumor bed. Using these criteria, R0 resection in the West is associated with a relapse rate of 52%. The majority of relapses (60%) are local (locoregional, lymph nodal, or peritoneal), while only 40% are hematogenous. Recent metaanalysis has documented that, at least for stage II and stage III disease, extended lymph node dissection can improve the radicality of the treatment and decrease the rate of recurrence. There is therefore a case for modifying the definition of an R0 resection by including other criteria. The Maruyama index [3], for example, estimates the likelihood of residual nodal involvement for each regional lymph node station. Patients with a low Maruyama index (<5) have a significantly increased survival.

The need to ensure that an R0 resection is performed is enhanced by the increased use of induction therapies. A significant benefit on survival and recurrence rate has been documented for preoperative chemotherapy. Selection of treatments for each patient will be increasingly refined, not only as predictors of response using biological imaging are developed but also as prognostic predictors of biological markers of gastric cancer are introduced. There is therefore a need to standardize the concept of an R0 resection such that outcomes from different centers can be compared and audited to ensure the best possible results are achieved.

#### *Splenectomy and/or pancreatectomy: H. Hartgrink*

The rationale for splenectomy in proximal gastric cancer is supported by extensive retrospective data from Japan

documenting a rate of 20%-30% positive lymph nodes in splenic hilum. However, recent RCTs have clearly documented that splenectomy and/or pancreatectomy routinely performed during total gastrectomy for proximal cancer carries a higher rate of postoperative morbidity and mortality. There are nine trials on splenectomy (three high-quality RCTs and six low-quality RCTs or retrospective comparative studies) and seven on pancreatectomy (one comparative and six noncomparative) undertaken as a standard maneuver during total gastrectomy for cancer of the proximal third of the stomach. The results show that both splenectomy and pancreatectomy do increase morbidity and mortality rates without leading to better survival; therefore, the pancreas and spleen should be removed only if there is direct invasion by the primary tumor.

#### *Reconstruction: A. Sandler*

Different problems are observed following gastrectomy. These include the loss of reservoir function and duodenal continuity, esophageal reflux, and adverse effects on hematopoiesis. Therefore the important components for reconstruction techniques are the creation of a substitute reservoir function, avoidance of gastroesophageal reflux, and minimal postoperative morbidity. Studies have compared the effect of preservation or exclusion of duodenal continuity on the mixture of chyme with biliary and pancreatic secretions, calcium/iron absorption, and lipid/protein digestion, with variable results. The role of reconstruction procedures after total gastrectomy using jejunal pouches has been studied in comparison with standard Roux-en-Y reconstruction. There appears to be little benefit for weight gain and slight improvement in quality of life which is also only apparent some time after surgery. However, the published series are small and there is no consensus on the preferred method of reconstruction. There is therefore a need for carefully designed studies to evaluate the role of the re-establishment of duodenal transit and the most effective pouch-reconstruction technique.

#### *Minimally invasive surgery: F. Corcione and P. McCulloch*

Since the first report of laparoscopic distal gastrectomy performed by Goh in 1992 [4] the adoption of minimally invasive techniques in gastric cancer surgery has developed worldwide. The reported experience has suggested that minimally invasive surgery of gastric cancer can be completed safely, may restore quality of life faster, and appears to be adequate cancer surgery as compared to standard open surgery. The technical component of esophago-jejunostomy after total gastrectomy requires further study. However, small individual center experi-

ence and limited numbers of trials preclude definitive conclusions. Therefore, there should be a systematic approach to training and meticulous outcome data recording and audit in order to determine for which patients minimally invasive surgery is indicated. This would be facilitated by a registry of minimally invasive gastric surgery across Europe.

*Prognostic markers—prediction of nodal involvement: role of translational research: D. Nitti and N. van Grieken*

Generally in cancer treatment, research is determining the role of prognostic markers in identifying novel therapeutic strategies, improving selection for treatment, and predicting prognostic risk. Cancer is a multifactorial process and therefore basic science needs the sophisticated technology of, for example, gene microarray analysis to overcome the limitations of single biomarkers. To date, the increased expression of the biomarkers E-cadherin, p53, *cerbB2*, epithelial growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and thymidilate synthase is associated with a poorer prognosis. Microsatellite instability has been shown to be associated with a better prognosis. Nitti reported experience of the identification of a combination of three genes which were associated with a higher risk of lymph node metastasis.

Progress in this area is slow and has been limited because sample sizes have usually been small, studies have had conflicting results, and positive results have not been validated appropriately, and often results have not been presented in the context of established prognostic systems such as TNM. Both Nitti and van Grieken emphasized the need to have standard approaches to clinical and laboratory processes and data collection and analysis. There must be close and cooperative collaboration between clinicians and basic scientists so that clinical material can be collected in large enough population samples to produce meaningful results. It will be only by such joint work that clinically useful markers will be identified to achieve the aim of personalized treatment.

### Summary

1. There needs to be an agreed definition of an R0 resection.
2. There needs to be standardization of lymphadenectomy to ensure the prognostic effect of nodal involvement can be most usefully assessed.
3. Treatment should be tailored according to disease status and patient factors.
4. Studies of reconstruction after gastrectomy should be developed.

5. Approaches to treatment and outcome need to be standardized for both audit and support for translational research.
6. Translational research should be fully supported to enhance the prediction of nodal disease and prognosis.
7. A registry of minimally invasive surgery should be established to define the place of the technique in gastric cancer management. Active support should be available from experienced centers for those beginning the procedure.

### Esophago-Gastric junctional cancer

*Classification and staging: C. Wittekind and G. Verdecchia*

The definition of the esophago-gastric junction is a complicated issue, as it is considered differently by anatomists, physiologists, and endoscopists. As the malignant potential of Barrett's metaplasia has been more understood and the appreciation has been gained that gastric cardia and subcardia cancers are different entities, it has been important to review the pathology, not only for staging but also for treatment, particularly with regard to lymphadenectomy.

Siewert's classification of type I, II, and III junctional cancer is a topographical anatomical classification based on the position of the center of the tumor in relation to the esophago-gastric junction, and has been widely adopted [5]. The TNM sixth edition considers type I to be esophageal and type III to be gastric and classifies nodal metastasis accordingly. Type II cancers are considered within the gastric category, with lower mediastinal paraesophageal, paracardial, left gastric, and celiac axis nodes regarded as N1. However, there can be difficulties for cancers which involve both esophagus and stomach, as those with full-thickness penetration of the esophageal wall are T3, but those with full-thickness penetration of the stomach are T2b. Furthermore, celiac axis nodes are N2 for the gastric component, but M1a for the esophageal. Wittekind suggested that regional nodes including celiac axis nodes should be N1 if one to three nodes are involved and N2 if four or more nodes are involved. Furthermore, with the increasing use of neoadjuvant therapies the biological effect on the tumor needs to be taken into account.

The existing differences in number of nodes examined in the American Joint Committee on Cancer (AJCC) system and the tumor location in the Japanese system need to be appropriately included. The forthcoming TNM seventh edition is planned to address these issues.

*Treatment—surgery: H. Stein*

The approach to the surgical management of type II junctional cancers raises a number of key issues: the extent of lymphadenectomy, the length of the proximal esophageal margin, and the management of early lesions. The experience from Munich has established the pattern of nodal spread from junctional cancers. For type I cancers, spread is both cranial, involving mediastinal nodes in almost 10% with low mediastinal paraesophageal nodal metastases in 31.5%, and caudal to intraabdominal nodes. For type II and III tumors the rate of mediastinal nodal disease is very low—approximately 2%—with lower mediastinal paraesophageal nodes being involved in 15.6% and 12.1%, respectively. Therefore the preferred nodal dissection for type II cancers includes the lower mediastinal paraesophageal nodes with the N1 and N2 nodes for the conventional D2 procedure. This can be achieved by an extended total gastrectomy with distal esophagectomy. Furthermore, the Munich series has a very low anastomotic recurrence rate as long as the proximal resection margin is microscopically clear.

Management of early junctional cancers should be planned according to the local extent of the tumor, which is best determined by endoscopic ultrasound. If there is HGD or the tumor only involves the mucosa and is focal and small, EMR is possible. Invasion into the submucosa and multiple foci of disease are indications for limited surgical resection by proximal partial gastrectomy. Radical resection with lymph node dissection is indicated for T2 cancers.

*Minimally invasive approach: P. Nafteaux*

The development of minimally invasive esophagectomy (MIE) has been stimulated to determine whether the existing results of open surgery can be improved. In theory, the minimally invasive techniques should be less demanding for the patient and as a result there should be less blood loss, quicker return to normal gastrointestinal function, faster recovery with shorter hospital stay, and improved quality of life. However, it is also essential that the same extent of resection as that with an open approach is achieved. There are a number of small personal series which have shown that the procedure is possible with apparently equivalent outcomes to open surgery. Nevertheless, a number of important questions remain, particularly with regard to the most appropriate procedure; the selection of patients, not only in terms of their stage of cancer but also in terms of their suitability for the technique; and the training and experience of the surgical team. Nafteaux concluded that MIE is essentially minimal access rather than minimally invasive surgery. There needs to be much more work to evaluate and define its role, and this must include com-

parison with open surgery performed in the context of enhanced recovery programs, as well as considering randomized comparisons which must take into consideration the hospital costs.

*European Junctional Cancer Registry: J. Kulig*

Kulig proposed the establishment of a European registry to facilitate comparison of data between different institutions treating junctional cancers. By recording an appropriate dataset for individual patients and entering it onto a database it would be possible to evaluate many of the controversial aspects of the treatment of these tumors to reach a consensus and establish standards for surgical treatment.

*Summary*

1. There needs to be a validated staging system for esophago-gastric junctional tumors.
2. The treatment of type II junctional disease needs to be standardized with regard to lymph node dissection, distance of resection margins, and management of early disease.
3. A standardized approach may be facilitated by the establishment of a cancer registry for junctional cancers which will allow inter- and intracountry comparisons and audit.

**Multimodal therapy of gastric cancer***Neoadjuvant and adjuvant therapies: C. Pozzo, V. Valentini, and P. Sugarbaker*

Because more than 60% of patients present with stage III or IV disease with a 5-year survival of 20% or less, surgery needs to be combined with other therapies to improve the outcome for the majority of patients.

Recently the United Kingdom Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial and the French Federation Francophone de Cancerologie Digestive (FFCD) trial have both shown a survival advantage for pre- and postoperative chemotherapy of approximately 13% in comparison to surgery alone [6, 7]. These trials have confirmed the feasibility of administering preoperative chemotherapy without excess postoperative morbidity. In both trials there has been a biological effect with downsizing and downstaging the tumor and enhancing the chance of performing an R0 resection. As a result there has been better local control and reduced rates of systemic relapse. It has been concluded that preoperative chemotherapy should be the new standard of care for patients with operable locally advanced gastric or esophago-gastric junctional cancer.

These trials have raised a number of questions which need further evaluation. Firstly, there is a group of patients who do not respond to chemotherapy. It is important to identify this group, as there may be a case for proceeding to early surgery rather than completing the prescribed course of preoperative treatment. Secondly, in both trials, just over 40% completed the postoperative cycles of chemotherapy and it is not clear if this is necessary. Analysis was on an intention-to-treat basis, so it is not possible to compare the outcome of those who completed with those who did not. Thirdly, in both trials, the postoperative treatment was given for three or four cycles. Future endeavors should consider assessing better chemotherapy regimens, integrating targeted agents, and integrating radiotherapy.

The combination of chemoradiotherapy is attractive, as the chemotherapeutic agents sensitize tumor cells to the effect of radiotherapy [8]. The United States Intergroup trial 0116 demonstrated a survival advantage for those treated with adjuvant chemoradiotherapy. However, this trial has received criticism for the high proportion of patients undergoing limited surgery. A fundamental part of any study with adjuvant radiotherapy is to ensure careful quality control of the radiotherapy planning. Valentini argued that radiotherapy should be considered in the adjuvant setting in patients who have had an R1 or R2 resection, those who have had an R0 resection yet are considered at high risk because of concern about the adequacy of the surgery, and those who have had an R0 resection but have a high risk because of a high nodal burden.

The role of preoperative chemoradiotherapy has been evaluated in esophago-gastric junctional cancers in the POET study [9]. In the treatment arm there was a greater complete response rate with an improved survival; however, operative morbidity and mortality were greater, particularly in the group requiring thoracotomy. Such an approach requires further evaluation to determine whether it can improve on the current perioperative chemotherapy approaches.

The evidence thus confirms the benefit of chemotherapy and radiotherapy and there is a strong case for tailoring treatment according to the patient. However, it is essential that such multidisciplinary approaches are undertaken in the context of written guidelines, with careful discussion to assess the outcome for both individuals and groups of patients, and meticulous data documentation to ensure the quality of the different procedures.

Peritoneal involvement can present as clinical peritoneal metastases or with positive cytological washings without obvious evidence of peritoneal disease. A meta-analysis of ten randomized trials on adjuvant intraperitoneal chemotherapy demonstrated a significant survival benefit when hyperthermic intraoperative or postopera-

tive intraperitoneal chemotherapy was administered in patients with extensive serosal disease and with high-volume nodal disease. However, such treatment was complicated by a higher risk of intraabdominal abscess formation and neutropenia.

In selected patients with established peritoneal seeding, intraperitoneal therapy combined with gastrectomy and peritoneal resection can be beneficial. These results come from small series and have been compared with historical controls. There is thus a case for phase III trials to evaluate this approach further.

*Prediction of response—biomarkers: N. van Grieken and D. Roukos*

The use of chemotherapy and radiotherapy as adjuncts to surgery in gastric cancer is now well established. However, their use has been based on clinical trials in which all patients have received the protocol treatment. There is a need for better understanding of gastric cancer biology to facilitate more individualized treatment to maximize benefits yet minimize side effects.

Currently, the biological assessment of response is based on histopathological examination after surgery, on endoscopic biopsies, or at autopsy. These are crude measures of reduction in tumor size or tumor stage. The options for biological markers include serum markers and molecular markers reflecting cell proteins detectable in biopsies or shed into the serum from dying cells or changes in cell nuclear molecules and gene profiling. The complexity of gastric cancer implies that molecular markers are likely to be needed in combination, as opposed to a single agent. Furthermore, the complexity of each individual genome increases the variation in changes at the molecular level.

Roukos proposed different strategies for different stages of gastric cancer. For premalignant lesions and early-stage cancer, there need to be novel biomarkers to predict risk to enable preventative measures and to identify those treated by local resection. In stage II disease, biomarkers would help differentiate those for surgery alone and those for surgery and chemotherapy. In those with stage III disease, biomarkers would also be helpful for predicting risk but could also be used to act as predictors of response to chemotherapy. Finally, in stage IV disease, biomarkers could be investigated as targets for novel therapies. A collaborative endeavor with comprehensive tissue banks and standardized clinical information will provide the most effective approach to enable personalized preventative and therapeutic interventions.

*Imaging: K. Ott*

The most promising clinical method to assess and predict response to therapy has been biological imaging with

positron emission tomography-computed tomography (PET-CT) scanning. Ott described how the reduction in fluorodeoxyglucose (FDG) uptake could predict response to chemotherapy within the first 2 weeks of starting treatment. This has enabled the identification of responders and nonresponders and has had practical implications. Responders have completed the planned chemotherapy regimen and have been shown to have a superior outcome. Nonresponders have been submitted to early surgery and have had better survival than the group who remained on chemotherapy but did not respond. The main experience has been in esophageal and junctional cancers. In gastric cancer there appears to be a variable effect, in that diffuse-type cancers do not take up FDG as readily as the intestinal type. However, this approach has the potential to differentiate between patients and allow tailored therapies. Further studies are underway to expand the experience but also to include other biological substrates which may improve scanning accuracy.

*Future trials: W. H. Allum, H. Hartgrink, and A. Garofalo*

In the United Kingdom the Medical Research Council (MRC) clinical trials unit has initiated a multicenter study (ST03) to evaluate the addition of the anti-VEGF monoclonal antibody bevacizumab to perioperative epirubicin, cisplatin, and capecitabine (ECX). The control arm will be the same as the MAGIC treatment arm. During a phase II stage, 200 patients will be recruited and a formal review will assess the safety and feasibility of the regimen. The final aim is to recruit 1100 patients to detect a 10% increase of survival.

The Dutch group have launched the Chemoradiotherapy after Induction Chemotherapy in Cancer of the Stomach (CRITICS) trial to evaluate the benefit of postoperative chemoradiotherapy in association with preoperative chemotherapy. The preoperative regimen is based on MAGIC and the chemoradiotherapy includes administration of 45 Gy with capecitabine and cisplatin. The statistical calculation requires a sample size of 788 patients to show a difference of 10% in favor of the radiotherapy arm. As well as assessing the clinical effect, it is planned to collect tissue and serum for genomic profiling and proteomics to detect patterns of tumor recurrence and predict response to therapy.

A trial of hyperthermic intraperitoneal chemotherapy in high-risk gastric cancer has been proposed by Garofalo. Patients with serosal invasion, documented free intraperitoneal cancer cells, and node-positive disease will undergo D2 gastrectomy and be randomized to intraperitoneal chemotherapy and postoperative chemotherapy or postoperative chemotherapy alone. The main endpoint is overall survival, but secondary end-

points include local relapse—timing and site, treatment-related complications, risk factors for poor prognosis, and analysis of biological markers which predict risk of recurrence. It is planned to recruit 139 patients to detect a 22% improvement in survival.

### *Summary*

1. Biomarkers which can be used to predict prognosis and response to different treatments need to be developed. This can only occur with close collaboration between clinicians and basic scientists.
2. Biological imaging techniques need to be carefully evaluated in conjunction with clinical trials.
3. Currently recruiting trials should be supported in order to complete in a timely fashion.
4. The development of new trials should be actively pursued, using the European Network to present, discuss, and refine new proposals.

### **Quality of life**

*Quality of life—definition and measurement: T. Kuchler*

From the patient's perspective there are four key issues relating to the diagnosis of cancer. These are the nature of the diagnosis itself, the likely treatment, the overall survival after treatment, and the effect the whole process will have on their quality of life. The definition of quality of life is variable depending on their state of health. Aristotle said of quality of life "... and often the same person changes his mind: if he gets sick, then it is health, and if he is well, then it is money." It is very much a conceptual topic and can be equated with satisfaction, which Hofstatter suggested was a ratio between the evaluation of what you have and your expectation of life.

In the context of health, quality of life has physical, mental (including emotional and cognitive facets), interpersonal, socioeconomic, and spiritual dimensions which are all subjectively interrelated. Increasingly, quality-of-life measurement has become a key indicator of the outcome of cancer care. The technical aspect of such measurement has been considered in two parts. The measurement is questionnaire-based; these questionnaires cover generic issues and, secondly, disease-specific topics. The generic components allow comparison of the impact of different diseases, whereas the specific components are more individually focussed. The European Organization for Research and Treatment of Cancer (EORTC) has produced a series of cancer site-specific questionnaires which have been validated in large populations and are the most useful types of measurement. In future trials, quality-of-life measurement

should be mandatory, particularly in gastric and esophageal cancer, where survival results and treatment side-effects are so varied.

*Nutritional support—perioperative supplementation via feeding jejunostomy: U. Bolder*

Weight loss is a progressive process in many patients as they recover from major upper gastrointestinal cancer surgery. Immune stimulation is a novel and theoretically attractive approach to overcome the immune-suppressive effect of major surgery. A series of patients received jejunostomy feeding with either an immune-enhancing diet or had standard enteral feeding after D2 gastrectomy. The test group continued with an immune-enhancing diet for 6 weeks postoperatively, whereas the controls could use vitamin supplements as they wished. The treated group had fewer overall complications and specifically fewer respiratory complications, maintained their body mass more effectively, and had a better quality of life. This was a small study, but it has raised a number of questions, including the relationship between postoperative weight loss and longer-term survival, the optimal enteral feeding regimen, and measures to minimize morbidity from feeding jejunostomy tubes.

*Cachexia from gastric cancer: F. Pacelli*

Cachexia associated with cancer is a debilitating process which not only impairs quality of life but also reduces

response rates to chemotherapy regimens. The main characteristic is a loss of lean body mass, which is a result of an imbalance between protein synthesis and protein degradation. A number of factors have been proposed which mediate this imbalance, including ubiquitin, which affects skeletal muscle proteolysis; increased muscle proteasome activity; and skeletal muscle apoptosis. Both ubiquitin expression and proteasome activity appear to correlate with disease severity in gastric cancer, although apoptotic rates do not seem to be predictive. Ideally, treatment would be enhanced by an agent that improves the appetite, inhibits different proteolytic pathways, and stimulates anabolism in skeletal muscle. Initial results with nutritional supplements rich in fish oils and immune-enriched diets are encouraging, but further studies are required.

*Summary*

1. Quality-of-life measurement should become an integral component of the management of patients treated for gastric or esophageal cancer.
2. The role of nutritional support needs further investigation, both in terms of clinical studies and also for achieving greater understanding of the molecular changes associated with reduced nutrition in patients with gastric cancer.

## Appendix

*Faculty*

William Allum (UK)  
 Giorgio Arcangeli (Italy)  
 Francesco Tonelli (Italy)  
 Hugh Barr (UK)  
 Ulrich Bolder (Germany)  
 Nicole van Grieken (Netherlands)  
 Marco Catarci (Italy)  
 Ha van Quyet (Viet Nam)  
 Jan Kulig (Poland)  
 Francesco Corcione (Italy)  
 Maurizio Degiuli (Italy)  
 Giovanni De Manzoni (Italy)  
 Christian Wittekind (Germany)  
 Domenico D'Ugo (Italy)  
 Alfredo Garofalo (Italy)

Giorgio Giannone (Italy)  
 Francois Gilly (France)  
 Peter Gunven (Sweden)  
 Pradeep Bhandari (UK)  
 Bertram Ilert (Germany)  
 Eric Jansen (Netherlands)  
 Thomas Kuchler (Germany)  
 Dimitrios Roukos (Greece)  
 Peter McCulloch (UK)  
 Hans-Joachim Meyer (Germany)  
 Stefan Moenig (Germany)  
 Marcella Mattolese (Italy)  
 Philip Nafteaux (Belgium)  
 Donato Nitti (Italy)  
 Katja Ott (Germany)

Paul Sugarbaker (USA)  
 Fabio Pacelli (Italy)  
 Henk Hartgrink (Netherlands)  
 Jose Trinidad Soares (Portugal)  
 Vincenzo Valentini (Italy)  
 Pompiliou Piso (Germany)  
 Carmelo Pozzo (Italy)  
 Giorgio Verdecchia (Italy)  
 Franco Roviello (Italy)  
 Takeshi Sano (Japan)  
 Aldo Scarpa (Italy)  
 Christoph Schuhmacher (Germany)  
 Andreas Sessler (Germany)  
 Hubert Stein (Germany)

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