An Overseas Perspective of Evolving Gastric Cancer Practices in Japan

To the Editor:
I have recently had the opportunity to visit the National Cancer Centre Hospital (NCCH) in Tokyo, and like my predecessors will offer a brief on the current perspectives of gastric cancer surgery in Japan.

Epidemiology Affords Experience
Gastric cancer is a common but curable disease, achieved only by surgical and, arguably, endoscopic means. It is the most common of all newly diagnosed cancers in the Far East although it is superseded by lung cancer in terms of cancer-related death (1). This is attributable not only to a rising incidence of lung cancer but also to improvements in gastric cancer care reflected in a steady increase in survival rates. The Far East now contributes to 56% of the gastric cancer burden of the world. Whilst adjusted incidence rates are declining, the age cohort of the general population is increasing, leading to no change in the absolute prevalence of gastric cancer. The patient demographic for gastric cancer in Japan also continues to change.

It is intuitive, therefore, that surgeons in the Far East have the greatest knowledge of this disease and experience in its management. However, routine clinical practices in the Far East continue to court controversy, particularly in Japan with its widely publicized methodologies. Such practices may be respected or admired but are not universally accepted, and the worldwide ambivalence resides at many levels. There is due acknowledgement that dedicated surgeons and units encountering large volume workloads will reap the benefit in terms of reduced mortality and morbidity rates and improved survival for their patients (2,3). In contrast, these admirable results have been viewed with scepticism. The reasons cited include a different patient population and a different disease in its stage and site distribution. In addition, a lack of prospective randomized controlled trials (RCTs), the current paradigm for all clinical research, has not offered support for the results of clinical practices in Japan which are deemed not to be transferable to a Western population (4).

Guidelines for Gastric Cancer Care
The Japanese Gastric Cancer Association (JGCA) continues to amend its General Rules for Gastric Cancer Study, first published by the Japanese Research Society for Gastric Cancer (JRSGC) in 1962 with editions in English from 1973 (5,6). It is currently on its 13th edition (7). From this has evolved the Guidelines for Gastric Cancer Treatment in Japan (8). Both documents are detailed, consistent and unambiguous. They are clinically applicable to routine practice and divide the management of gastric cancer into its component parts, i.e. treatment of the tumor, the lymphatic system, appropriate reconstruction and even permitted options for modifications such as laparoscopy, limited resections and endoscopic surgical dissection. These Rules and Guidelines provide a framework for care, in particular the surgical care of gastric cancer, and a common basis for stage-orientated treatment decisions. This results in the ability to separate a very heterogeneous disease into homogenous subgroups which may be enrolled into identical treatment protocols within the group, allowing for a meaningful analysis of outcomes.

This philosophy hinges on the steadfast belief that only through complete surgical excision of the tumour and its draining lymph node basin will disease clearance be adequately effected. The basis of this is that the lymphatic system forms ‘protective’ tiers around a tumor and that the likelihood of lymph node disease may be calculated given any tumor location and its depth of invasion (9). Of course, this assumes that disease progression occurs in a step-wise fashion.

The Gastric Division of the NCCH is one of the main protagonists in effecting these guidelines and the epitome of a highly evolved program of surgical care for gastric cancer patients. Whether or not its philosophy finds universal accord, it receives due respect for its consistency in practice. For so long there has been criticism of ‘over-aggressive’ surgical practices for gastric cancer, including the historic Appleby’s operation, left upper abdominal evisceration and more recently the stance on pancreatectomy, splenectomy and extended lymphadenectomy. However, having spent considerable time standardizing the extent of surgical resection to tumor excision and a D2 lymphadenectomy, the NCCH now ‘tailors’ surgery to the individual patient, even contemplating lesser degrees of surgical insult such as pylorus preservation, segmental resections and proximal gastrectomy.

Converging Standards of Practice
In contrast, D2 lymphadenectomy is not uniformly practised in the West. Although the USA have recommended this, guidelines in the UK do not advocate a ‘Japanese’ style practice outside of a trial setting (10). The rationale, safety and survival benefit of D2 lymphadenectomy have been questioned, and any advantage is offset by the high morbidity and mortality particularly associated with pancreatectomy and splenectomy.
The toxicity of treatment is perceived to be too high and even a ‘limited’ D1 dissection comes at a price, as shown by the UK Medical Research Council (MRC) and Dutch gastric cancer trials (11,12). However, these data cannot be translated into Japanese practice. Beyond the differences in disease and patient demographics, these trials have been criticized for a lack of ‘quality control’ over the surgery and pathology, with too many institutions contributing too few patients, and surgeons failing to reach a consistently acceptable point on the learning curve.

In spite of these RCTs, some gastric cancer surgeons in the West now routinely perform a gastrectomy with a D2 lymphadenectomy. More recent series in both the USA and the UK demonstrate that specialist institutions can achieve results approaching those of the Japanese on a stage for stage basis (13–16). However, until more RCTs are produced, the much-maligned MRC and Dutch trial data will continue to form the basis of an argument against the routine use of D2 gastrectomy.

It is evident that there is some convergence in the standards of care between the NCCH and those specialist centers in the West with a greater volume of gastric cancer work. There are reassuringly similar practices including the establishment of multi-disciplinary meetings, a lower threshold for endoscopy, meticulous pre-operative staging and preparation, operative techniques and multi-disciplinary teams in the post-operative delivery of care. Dedicated high volume centers have paved the way for a reduction in rates of mortality and morbidity with improvements in overall survival. However, there is some way to go before a national operative mortality figure comes close to that of 2% and <1% for specialist centers in Japan (17,18).

Why is there still such a discernible gap? Still the argument holds that patients are fitter, biologically younger and on the whole have earlier stage disease. Even allowing for stage differences, survival curves and stage migration are permitted by the differences between the Japanese and TNM/UICC classification systems for gastric cancer (19,20). Moreover, upper gastrointestinal surgeons in the UK continue to contend with an emergency workload, benign upper gastrointestinal disorders and esophageal cancer surgery which would normally lie within the remit of a different division at the NCCH.

**EVOLVING GASTRIC CANCER CARE AND TRIALS IN JAPAN**

Many institutions in Japan now possess a mature and highly evolved standardized practice for gastric cancer from which individually tailored care may be applied. Any visitor to the NCCH will encounter this principle on a daily basis, with routine procedures including pylorus-preserving gastrectomy, proximal gastrectomy with jejunal interposition, and extended lymph node sampling or sentinel lymph node mapping within a trial setting. These practices are governed by stringent criteria, established algorithms of care, and require meticulous documentation at all stages including diagnosis, staging, surgery and pathology. Only with a robust data set and a high throughput will the audit process permit such a rapidly evolving practice.

Moreover, the subspecialist divisions at the NCCH are organized into functional units, and specifically for the gastric division this will include Endoscopy (diagnostic, staging and therapeutic endoscopic mucosal resection), Upper Gastrointestinal (GI) Radiology and GI Pathology. The training of junior surgeons within the residency program also rotates on a functional basis to include the above divisions plus the related subspecialties of Hepato-Pancreato-Biliary and Esophageal Surgery, and anesthesia for the patients within these departments. This enviable organizational machinery is the result of an evolutionary process from which there is now a major emphasis on the establishment of clinical trials.

Japanese gastric cancer surgeons have been confused and perturbed by the RCTs from the West since they lie in discord with their belief in the benefits of radical lymphadenectomy. Whilst they acknowledge their huge contribution, they have concerns regarding the quality of data resulting from a treatment with an unacceptably high toxicity by Japanese standards, however robust the analytical methods may be. These RCTs are not translatable into Japanese gastric cancer practice and there is now an acceptance and acknowledgement of the differences in patient and disease demographics, and differing philosophies and regimens of treatment. As such, the Japanese will take ownership of their data from highly specialized, experienced, large volume institutions based on robust audit processes, in order to generate their own evidence-based practice, dispel criticisms and ultimately provide a rationale for the practice of and amendments to the existing General Rules and Guidelines.

In this regard, Japan has developed a formidable machinery—the Japanese Clinical Oncology Group (JCOG). This was first founded in 1978 from a research grant and given its current title and state funding from 1990. It contains 13 disease-related subgroups and encompasses institutions across Japan in the participation of national trials. The division of JCOG specific to gastric cancer surgery now contains 29 institutions with stringent entry criteria in terms of volume and standards of practice. Data gathering is closely monitored at all stages. With this, Japanese clinical research has attained the standards of evidence-based medicine acceptable to Western practice. Current JCOG trials specific to gastric cancer include those on splenectomy (JCOG 0110) (21) extended lymphadenectomy (JCOG 9501) (22), a sentinel node mapping feasibility study (JCOG 0302), and numerous chemotherapy trials, all conducted on an enviable scale.

In November 2004, the NCCH hosted the Inaugural Symposium of Asian Clinical Trials for Gastric Cancer. It was a privilege to witness the high levels of cooperation between different centers within the participating countries of Japan, Taipei, Hong Kong and Korea, the latter of which has a centralized gastric cancer practice that dwarfs even that of Japanese standards. The remit of this meeting was to establish an international consortium through which multi-center trials can be conducted initially using the machinery of the
JCOG but eventually to have its own international Clinical Oncology Group specific to gastric cancer. This will clearly shorten the trial time in order to keep apace of the necessary changes in gastric cancer care. Eventually, this body will seek to include China which currently accounts for an estimated 41% of the gastric cancer burden of the world.

Whilst the concept is ambitious, it will take evidence-based practice for gastric cancer care to a higher level. Ultimately, as surgical practice parallels the advancement of clinical research in Japan and her neighbors, the world may need to look to the East for the answers in the future management of gastric cancer patients.

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References