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INTRODUCTION

REPORTS ON cure rates above 50% after radical surgery for gastric cancer in Japan, have for decades impressed Western surgeons, whose results largely have remained poor. Some Western authors have, however, also been able to present historical series with 5-year survival data well above 50% when following Japanese recommendations [1–4]. Different views on the role of lymph node dissection are presented above [5,6]. Some reasons for the apparent discrepancy warrant reconsideration, as the different views are based on the same accumulated clinical data (Table 1).

IS THE BIOLOGY OF GASTRIC CANCER SIMILAR IN JAPAN AND WESTERN COUNTRIES?

Gastric cancer is very common in Japan, where it remains the leading cause of cancer death [7], in contrast to Western countries, where the incidence is decreasing. In Japan, there are cost effective, large-scale screening programmes, where as many as 40–50% of early cases are diagnosed at an asymptomatic stage [8]. The differentiation between benign dysplasia and early invasive cancer is, therefore, potentially a greater problem in Japan [8]. Japanese pathologists also have more experience in handling such borderline cases. The predominant histology tends to be of the Lauren intestinal type in Japan, in contrast to diffuse type in Western countries [7,9]. A stronger association between *Helicobacter pylori* and intestinal type cancer (>85%) than diffuse type cancer (32%) may also be of relevance [10,11]. A stepwise development from normal mucosa via atrophic gastritis, incomplete metaplasia, dysplasia and cancer has been proposed, where all stages are influenced by preventative or risk factors [12]. Such factors seem to be influenced by the environment.

An increasing frequency of proximal tumours of more aggressive nature with poorer prognosis is emerging in Western countries, which may partly mask a possible benefit exhibited by better surgery [13,14]. The relative increase of gastric lymphomas may also be a problem, as the differentiation between a malignant lymphoma and a diffuse adenocarcinoma may be difficult [15].

Directly comparing gastric cancer patients treated in Japan and in Germany, there were several important differences in univariate analyses, but even for patients with similar prognostic factors there was a clear survival difference [16]. An important prognostic factor was the centre itself. It is difficult to draw firm conclusions, but any difference ascribed to the biology may, therefore, be confounded by diagnostic and therapeutic procedures. The difference in biology is presumably so small that it cannot account for the observed survival differences.

THE PATTERN OF SPREAD FOR GASTRIC ADENOCARCINOMA

Gastric cancer may principally spread by four routes: (1) By direct extension into neighbouring structures; (2) Lymphatic spread to neighbouring lymph nodes (the main route, although a few tumours metastasise directly to distant nodes [17]. This pattern is much more common (approximately 70%) than generally clinically noticed during an operation (approximately 20%) [18]. Furthermore, micrometastases may be found when systematically looked for in approximately 10% of N₀ patients [4] or by special search for cytokeratin in tumour cells by antibodies [19] or mRNA [20]; (3) Peritoneal spread is mainly associated with serosal invasion of the primary tumour [21]; (4) Distant spread, mainly haematogenously to liver and lungs. The extent of gastric resection is generally agreed upon, but the main controversy is related to the benefit and risk of dissection of lymph nodes beyond the perigastric lymph nodes.

THE ROLE OF SYSTEMATIC LYMPH NODE DISSECTION

To evaluate the difference between systematic lymph node dissection of secondary lymph node stations (D2 type dissection) and the more limited removal of perigastric lymph nodes only (D1 dissection), historical experience has to be considered. From a scientific point of view, randomised trials are the preferred method. Two such studies have been performed, but final analyses have not yet been published. The Dutch study, including 1078 patients, showed high operative mortality (10% versus 4%) and complications (43% versus 25%) for D2 resections compared with D1 resections [22]. Also, the British randomised study, including 400 patients, demonstrated increased mortality (13% versus 6.5%) and also overall postoperative morbidity (46% versus 28%) for D2 resections compared with D1 resections [23]. This reflects the trend towards the higher mortality rate observed in most Western series, whereas mortality is generally lower than a few per cent in Japanese series. The presented survival rates from the British study make it unlikely to demonstrate any benefit of D2 resections, mainly related to the morbidity and mortality of pancreatectomy associated with the performance of D2 resections. This can be related to the greater experience and exuberant technical skills of the Japanese surgeons [23,24]. The main objection towards the Dutch and the British randomised studies is that the surgeons had limited experience with D2 resections for patients included in the trials. The contribution of the patient's constitution may also play a role, as Western patients tend to be fatter and older than the Japanese patients, but this is probably of

Table 1. Some factors which may influence the apparent survival difference after surgery for gastric cancer between Japan and Western countries

Factor	Japan	Western countries
Incidence	High	Low
Screening	Yes	No
Asymptomatic early cases (T1–T2)	Yes (40–50%)	Occasional
Lauren type	Intestinal	Diffuse
<i>Helicobacter pylori</i>	37%	80%
Factors influencing the operative procedure		
Age	Younger	Older
Patient's constitution	Slim	Abdominal fat
Team experience	High	Limited
Operative mortality	Low, < 1(2)%	High, 5–13%
Lymph node dissection	D2 systematic resection	D1 perigastric lymph nodes only
Number of examined lymph nodes	High	Limited

marginal significance. When comparing 5-year survival, one should not overlook the fact that many case series give survival figures excluding peri-operative deaths, thus apparently improving the results by approximately 10% in Western series [25, 26]

It may seem strange that a systematic lymph node dissection will improve the prognosis of N₀ patients [27]. Careful histopathological examinations have, however, shown that the metastases tend to be small with gastric cancer and approximately 10% of patients have micrometastases [4, 19]. Thus, there is probably a subgroup where systematic dissection will remove microscopically disease which can easily pass unnoticed for the surgeons and pathologists. The better results obtained by the Japanese could in part be related to a more meticulous dissection as well as more thorough pathological examination. Japanese surgeons seem able to identify twice as many lymph nodes as specially trained Dutch surgeons [28]. The number of involved lymph nodes increased, when the yield by a formal D1 resection was compared with the information obtained by examination of the extra lymph node stations for a D2 resection [28]. The D2 resection may, therefore, contribute to a stage migration, where more early advanced stages are diagnosed, with apparent improved diagnosis stage by stage. A further apparent improvement of the results may emerge from the contribution of true early, asymptomatic gastric cancers, diagnosed in Japan by screening, which is rare in Western countries. Thus, part of the contribution to improved survival may be related to better diagnosis of lymph node metastases and part from more true early gastric cancers with inherent excellent prognosis.

HOW CAN WE IMPROVE THE SURVIVAL OF PATIENTS IN EUROPE AND OTHER WESTERN COUNTRIES?

As an oncologist, I have to admit that primary treatment of gastric cancer remains literally in the hands of skilled surgeons. No drug or radiation regimen has had a proven effect on survival. To improve the current results, I will focus on two aspects: better selection of therapy for early gastric cancer and centralising the handling of the patient group to augment the experience for the surgeons handling gastric cancer.

Early gastric cancer

The definition of early gastric cancer is tumours localised to the mucosa (T1) or submucosa (T2) [8]. Evidence accumulated from several decades has convincingly proved that

Japanese surgeons can cure early gastric cancer. The prognosis is excellent for T1, T2 and N0 tumours, but drops rapidly for T2 N+ tumours even in Western series [29]. It may be fruitful to define more detailed criteria for early gastric cancer patients, which do not need the risk associated with D2 or possibly also D1 dissection. For T1 cancers and small, i.e. < 2 cm, T2 cancers, there is a risk of 5–20% for lymph node spread [8, 30, 31]. A more conservative surgical approach, resection of perigastric lymph nodes (D1) [26] or simply endoscopic resections [30] may be an acceptable approach for selected patients in these groups (elderly patients?), if the pre- and peri-operative diagnoses reach sufficient accuracy [31]. Laparoscopic ultrasonography may possibly improve the diagnosis of early lymph node metastases [32].

Centralised gastric surgery

As discussed above, both the randomised Dutch and British studies exhibit the problem of a lack of training of the surgeons on a level comparable with that of Japanese specialised surgeons [22, 23]. Based on the vast experience from Japan, together with their high incidence, it seems currently only possible to present the final proof of the superiority of D2 resections versus D1 resection in Japan. However, their low operative mortality and excellent results from large series make it ethically difficult for them to offer their patients a possibly less efficient therapy. The Japanese data are currently based on case series with the inherent biases of this method.

In most Western countries, there will possibly be a gain by limiting the surgery for gastric cancer to fewer specialised teams, including pathology and postoperative care, to improve the survival of this dreadful disease. The consistent lower mortality rates with D2 resections in Japan can no longer be simply ignored. A realistic goal may be to improve the survival for all patients operated on for cure by 10–20%. I expect that in the near future the patients will have the right to know the mortality rate, morbidity and 5-year survival obtained at each institution offering their service or find it via the Internet! When sufficient experience has been obtained by centralised handling, the well-trained specialist Western surgeons should consider new prospective trials which can withstand the critique of the British and Dutch studies.

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