The new classification was developed, with four N categories (N0 to N3) instead of three as was initially proposed, and was presented in Seoul, Korea, at the 12th International Seminar of the WHO Collaborating Centre for Gastric Cancer in 1996 [9].

In addition to the change in N status, hepatoduodenal nodes are now once again regarded as regional nodal metastases rather than distant metastases, and the stage grouping has been altered, with all N3 patients now classified as stage IV (Table 2). T4N1 disease has also been changed to stage IV, having previously been classified as stage IIIb in 1987.

The latest edition of the TNM classification (sixth edition; 2002) amends pT2 into the subgroups pT2a and pT2b, which represent invasion confined to the muscularis propria and subserosa, respectively. This equates to T2 MP and T2 SS in the JGCA classification.

Japanese classification

The first edition of the General Rules for Gastric Cancer Study was published by the Japanese Research Society for Gastric Cancer in 1962. Stage groups were defined by the extent of serosal involvement (S stage), the location of involved lymph nodes depending on the site of the primary tumor (N stage), and the extent and sites of distant metastases (M, H, and P stages for distant metastasis, and hepatic and peritoneal disease, respectively). In its twelfth edition, the General Rules changed from the S-stage to a T-stage system, which was equivalent to the T-staging of the UICC system.

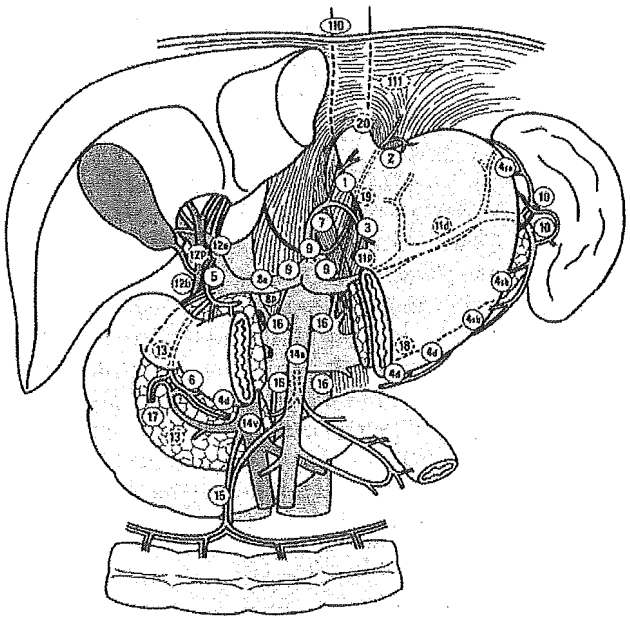

Fig. 1. Lymph node station numbers (*circled*) in the Japanese classification of gastric carcinoma [3]. These stations are further classified into N1/N2/N3 according the location of the primary tumor

The JGCA classification gives a number to all of the regional lymph node stations (Fig. 1), which are classified into three tiers according to the location of the primary tumor. Radical lymphadenectomy in gastric cancer surgery has long been commonplace in Japan and large databases of the incidence and sites of lymph node involvement exist, depending on the site of the tumor and its T stage. The purpose of the meticulous lymph node classification in the General Rules was therefore to guide surgeons to decide the extent and location of lymphadenectomy, so that any potentially involved nodes could be removed according to the site and depth of penetration of the primary gastric cancer.

Lymph node staging was characterized on the basis that gastric cancer metastasizes to groups of lymph nodes arranged radially around the stomach in tiers. The nomination of different lymph node groups to their respective tier was based upon the results of anatomical and physiological studies on lymph flow with different tumor sites.

Various amendments to the original classification followed, and the most recent classification is aimed at surgeons, pathologists, oncologists, and endoscopists who carry out endoscopic mucosal resection (EMR).

English versions were published in the *Japanese Journal of Surgery* in 1973 [10] and 1981 [11] and were referred to in Western studies. However, they were only a digest and could not fully convey the concept or details of the General Rules. The first comprehensive English edition was published in 1995 [12], based on the twelfth Japanese edition, and was named *Japanese classification of gastric carcinoma* (Table 3). The second English edition was based on the thirteenth Japanese edition, and was published in *Gastric Cancer* in 1998 [3].

There were a variety of changes in the most recent edition of the JGCA classification [13], such as rules for EMR and for staging carcinoma of the remnant stomach, and peritoneal cytology has been included in staging.

The most important changes in the current edition from a surgical point of view are the revision of lymph node staging and the consequent limitation of dissection level. Lymph node groups were reallocated from four tiers (N1 to N4) to three tiers (N1 to N3) on the basis of a detailed study of the effectiveness of dissection of different lymph node stations for tumors in the various locations within the stomach. Some lymph node groups, even some perigastric nodes for specific tumor locations, are no longer regarded as regional nodes if involved, but are regarded as sites of distant metastasis (M). This follows because their involvement is rare, and if it occurs, it invariably reflects a very bad prognosis [14]. One example would be the involvement of no. 2

Table 3. Japanese classification, 12th edition; 1993 (1st English edition; 1995 [12])

		P0, H0, M0				P0, H1, N0-2	
		N0	N1	N2	N3		
P0 H0 M0	T1	Ia	Ib	II	IIIa	IVa	
	T2	Ib	II	IIIa	IIIb		
	T3	II	IIIa	IIIb	IVa		
	T4	IIIa	IIIb	IVa		IVb (N4, P2,3, H2,3, M1, etc)	
P1, H0, T1-3		IVa					

Table 4. Japanese classification, 13th edition; 1999 (2nd English edition; 1998 [3])

		M0				M1
		N0	N1	N2	N3	
M0	T1	IA	IB	II	IV	
	T2	IB	II	IIIA		
	T3	II	IIIA	IIIB		
	T4	IIIA	IIIB	IV		
H1, P1, CY1, M1						

(left paracardial) nodes in the case of antral tumors. Other node groups, such as 14v (nodes along the superior mesenteric vein) and 12a (along the proper hepatic artery) are common sites of nodal metastasis for lower gastric tumors, and their dissection, even when positive, is often associated with survival. These groups have thus been brought into the N2 tier from the previous N3 tier. As a consequence, the D2 dissection, including all N2 node stations, is more radical than was previously the case, and is better targeted to actual rather than theoretical patterns of spread. D2 dissection can now be applied as standard surgical treatment for advanced gastric cancer. D3 dissection should be regarded as investigational treatment and is not standard. Following the revision of the N staging, there is no longer a category of "D4" dissection. The effect of the changes on stage grouping is that all N3 disease is regarded as stage IV, which is now no longer substratified.

There was a striking resemblance in the staging tables between the second English edition of the JGCA classification (Table 4) and the fifth edition of the TNM classification (Table 2), with the only difference being for the assignment of T4N1 disease, although the definition of N is totally different, as mentioned.

Evaluation and comparison

Similarities and contrasts between staging systems

Unification of staging systems or the concepts of staging is desirable and dialogue between Japanese and Western groups has resulted in alterations in both staging systems to take account of their different approaches.

In 1978, the UICC refined the anatomical-based N grouping into two tiers to reflect radial nodal spread, in keeping with the Japanese principles. N1 involvement was confined to perigastric nodes close to the primary, and N2 nodes referred to those along the hepatic, left gastric, splenic, or celiac arteries, as well as more distant perigastric nodes. This allowed some comparison between Japanese and UICC classifications, as N1 and N2 nodes corresponded to some extent across the two systems, although the anatomical details differed considerably.

The recent change of TNM staging to a number-based node status was a major turnaround that might separate irreversibly the two classifications, which had been converging. However, as far as prognosis is concerned, it has made direct comparison between Western and Japanese patients much easier, as the same data are available for both sets of patients. Now the clinical data recorded by the JGCA system can be exactly translated to the TNM system. The opposite is totally impossible, because the number-based system is a post-hoc pathological staging and bears no relationship to patterns of lymph node spread.

By contrast with the JGCA classification, which provides comprehensive and meticulous guidance to clinicians, the TNM classification is a simple staging system. There is little guidance on management, except that a minimum of 15 lymph nodes is recommended for accurate staging. The stage stratification from the TNM system is simple to apply and gives good prognostic information, but the use of lymph node number alone means that, without supplementary information, stage-dependent management cannot be practiced before final histology is available, as it is impossible to assess the exact number of positive lymph nodes radiologically or even surgically.

Differences in surgical philosophy between Japan and the West

It was Moynihan [15] who said that "Surgery of malignant disease is not the surgery of organs; it is the

anatomy of the lymphatic system". This is undoubtedly a basic principle of Japanese surgical practice. The commonest site of metastasis for gastric cancer is to lymph nodes. Japanese surgeons believe lymph node metastasis is orderly and progresses through the tiers of nodes in a stepwise manner. By defining the lymph node groups in each tier, the surgeon can remove all nodes to the level above that in which positive nodes are apparent or likely, on the basis of preoperative and intraoperative staging.

The JGCA classification is much more than a simple staging system, as it outlines a whole approach to gastric cancer. Rules are defined for diagnosis, surgical procedures, histology, and staging, as well as details of how to prepare the surgical specimen and lymph nodes. The JGCA classification details which node groups to remove depending on the site of the tumor and the level of dissection required. Stage grouping for prognosis naturally uses the same nodal tier basis for N-stage stratification, as it reflects both the spread of the disease and its treatment strategy.

On the other hand, the focus in Western surgical philosophy has been that prognosis is determined to a great extent by the biology of the primary tumor, and that lymph node metastasis is a marker of tumor dissemination [16]. Extended clearance of lymph nodes, unless obviously involved, is perceived to incur excessive morbidity with doubtful survival advantage. Thus, the TNM system places emphasis on prognostic staging and provides little treatment guidance.

Nevertheless, some European surgical groups consider the extended lymphadenectomy as an effective local tumor control and continue to employ D2 dissection and Japanese style N-staging [17].

Prognostic value

Japanese versus TNM classification. Since the introduction of number-based nodal staging in the UICC/TNM system, several Japanese authors have been able to compare prognosis by Japanese and TNM staging in the same patients.

In a study by Fujii et al. [18], 1489 patients were classified retrospectively according to the two classifications. They found that the survival curves in relation to the nodal staging of the two classifications were more or less similar, in that a decrease in survival was associated with an increase in the nodal classification. However, there was more homogeneity in the TNM stage groups than with the JGCA: when the patients with "n1" metastasis by the JGCA system were subdivided according to the TNM number-based system, there were significant differences in survival between "n1/pN1" and "n1/pN2". The same was true for JGCA "n2" patients classified as pN1 or pN2 by TNM stage. However, there was no difference in survival when each of TNM pN1 and pN2 groupings was subdivided into JGCA "n1" and "n2", i.e., patients with "pN1/n1" or "pN1/n2" shared similar survival curves, as did those with "pN2/n1" and "pN2/n2". This suggests that the prognostic impact of TNM pN stage is superior to that of JGCA "n" staging.

Ichikura et al. [19], Hayashi et al. [20] and Ichikawa et al. [21] also published their results from patients who underwent clinically curative gastric resection, using the JGCA and the fifth TNM classifications. All three groups of authors concluded that the TNM classification for lymph node involvement was superior to the JGCA classification in terms of homogeneity and prognostic value.

Similar conclusions were drawn by Kodera et al. [22], and they found that, even when lymphadenectomy was limited to perigastric lymph nodes, as in a standard Western style D1 resection, there was a difference in survival between pN1 and pN2, which supports the use of the new TNM classification.

In summary, therefore, the number-based N staging has greater prognostic power than the anatomical-based system.

Old TNM (1987) versus new TNM (1997) classification. Direct comparisons of the old and new TNM systems have been published by a variety of authors. Katai et al. [23] analyzed the results of 4362 patients who underwent resection for gastric cancer and found that the new system provided better prognostic stratification than the old system. However, patients classified as "pT4N1" in the new system fared better than other patients in stage IV and would have been better classified as stage IIIB.

Karpeh et al. [24] looked at the old and new AJCC/TNM classifications in 1038 patients, the majority of whom had undergone extended lymph node dissection; they also concluded that node numbers provided more homogeneous survival curves and better prediction of outcome than sites of metastases as defined by the 1987 AJCC/TNM criteria. These authors also strongly countenanced the minimum requirement of 15 nodes to limit stage migration.

Kranenbarg et al. [25] evaluated the old and new TNM classifications for their practicality and prognostic value, using the data of 1078 patients from the Dutch Gastric Cancer Trial. They found that the new (1997) TNM classification gave better prognostic stratification than the old (1987) classification.

The above studies differed from the conclusion reached by Mendes-de-Almeida et al. [26], who found the new TNM classification not very effective in improving the prognostic stratification of lymph node involvement when compared with the old TNM classification. A similar conclusion was drawn by de Manzoni et al.

[27], who concluded that both the site and the number of positive lymph nodes were independent prognostic factors in gastric cancer. Lee et al. [28] did not find superiority of the new classification, and questioned the validity of the current cutoff point for N-staging.

Practicalities of the classifications

Pre- and intraoperative staging. The TNM staging system was originally designed to help plan management before any treatment, and it is often applied in a preintervention setting, but offers little descriptive information on gastric cancer. Treatment planning often relies on supplementary information, in addition to the TNM or stage descriptor.

The recent change in TNM nodal staging further limits the ability to accurately stage patients before treatment. It is true that, in any case, the preoperative assessment of regional lymph nodes in gastric cancer using radiological imaging methods has a low accuracy rate, but counting involved lymph nodes radiologically is impossible, whereas identification of the sites of abnormal nodes is included within standard radiological reporting. Because neoadjuvant chemotherapy is attracting increasing interest today, the importance of pretreatment staging inevitably increases. The N-staging of the current TNM system does not function in this regard, and some modification might be required in the future.

The intraoperative findings during surgery may include macroscopic laparotomy findings, frozen section examination, cytology results, and the macroscopic findings of the resected specimen. Within the JGCA classification, there is clear guidance on the relevance of metastatic disease in the peritoneal cavity or any of the relevant lymph node groups, enabling surgical strategy to be decided on the basis of knowledge of the likely oncological outcome of the patient. While all the same information is available to the Western surgeon, TNM staging has little to offer in regard to strategy, unless frank, previously unrecognized metastases are found.

One example is positive peritoneal cytology, which represents stage IV disease by the current JGCA classification and is equivalent to distant metastasis in terms of prognosis. A positive finding will render a procedure palliative [29,30], and should restrict the need to pursue a radical resection.

Peritoneal cytology is not represented in the current TNM classification, and requires additional annotation if it is to be included in trials or treatment protocols.

Lymph node retrieval. The processing of lymph nodes is detailed and time-consuming with the Japanese system [31], and has been criticized for being complicated and unnecessarily labor-intensive, as it is performed by the surgical team. By contrast, in the West, the pathologist is in charge of the resected specimen, is often unaware of the precise location of the relevant lymph nodes, and is unlikely to be able to allocate each lymph node to its corresponding site and tier following an en-bloc resection. Now the number-based system can be easily applied in the West.

The TNM classification stated, in the fifth edition that, for pN0, "histological examination of a regional lymphadenectomy specimen will ordinarily include 15 or more lymph nodes". While many authors have supported the validity of the minimal number of 15 for staging [32,33], some surgeons have suggested that it could be reduced without influencing the prognostic analysis, thereby considerably reducing "unclassified (pNX)" cases. Kranenbarg et al. [25] suggested that a minimum of 5 consecutive negative nodes would suffice to stage gastric cancer as pN0, based on the data from the Dutch D1/D2 trial. Ichikura et al. [34] found that the survival rate for patients with 10 to 14 negative nodes was as good as the rate for those with 15 or more negative nodes, and suggested that the minimum number to be examined for pN0 could be reduced to 10.

In the latest edition of the TNM classification, the following sentence has been added to the pN0 definition: "If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0". This appears to mean that the figure of 15 is a recommendation, but no longer a requirement, for pN0 staging.

In node-positive patients, the current TNM classification may cause serious problems of underestimation. For example, if 6 lymph nodes only were retrieved, and all were positive for cancer cells, the staging would be assigned as pN1 in this system. It is highly likely that such a patient would have had further positive nodes that had been dissected, but not retrieved, and thus could have been staged as pN2 or pN3 if 16 or more nodes had been retrieved. This is not an unlikely situation in Western general hospitals; Mullaney et al. [35] assessed the number of lymph nodes documented for surgically managed patient in the West Midlands, United Kingdom, and found that only 31% of surgically resected patients could be staged with at least 15 nodes.

Furthermore, some authors have even suggested that 15 nodes may not be sufficient for accurate staging of metastatic nodes. Lee et al. [36] reported a retrospective analysis of 4789 patients with gastric cancer and suggested that, for advanced disease and in particular for stage IIIB, more than 15 nodes may be required for optimal staging. They indicated that, with a smaller number of nodes examined, there is a high possibility of underestimation and stage migration.

Ichikura et al. [34] emphasized that, though the mini-

mum number for pN0 could be reduced from 15 to 10, accurate staging of pN1 and pN2 requires the examination of 20 or more nodes, because the number of metastatic nodes was significantly correlated with the number of examined nodes.

Stage migration. The issue of stage migration, or the "Will Rogers phenomenon" [37], is frequently cited as a potential cause of differences in outcome between Japanese and Western patients [1]. Japanese patients undergo D2 dissection as the standard treatment, and, because more nodes are harvested, they are more likely to have positive nodes picked up compared to D0/D1 gastrectomy. The same patients in an extended lymphadenectomy series will thus be allocated a worse prognostic stage than their counterparts who had a D0/D1 gastrectomy. This will improve the survival data for all stages, purely by reallocation of patients with lymph node metastases into higher stages [38].

The introduction of the number-based N-staging may reduce stage migration among the groups with different extents of lymphadenectomy [39], if the resected nodes are fully retrieved. However, enthusiasm for nodal retrieval rather than extent of lymphadenectomy may directly influence the N-staging in this system.

Japanese surgeons usually retrieve as many lymph nodes as possible, because the nodes are literally their "harvest" of cancer surgery, while Western pathologists would be reluctant to retrieve more than the minimum requisite. The only means to prevent or minimize stage migration in the number-based system is to keep nodal retrieval at a high level (e.g., at least 15). Now that the minimum requisite of 15 is practically abolished in the sixth TNM edition, underestimation and consequent stage migration may further enlarge the apparent differences in treatment results between Japan and the West.

Other Classifications

Numerous classifications have been proposed by individual groups after sub-analysis of their own data. Most are adaptations of either anatomical or numerical systems of N-staging, as in the two major classifications.

Adachi et al. [40] and Whiting et al. [41] both employ anatomical nodal staging, with junctional nodes between conventional N1 and N2 tiers. Whiting et al. [41] suggested that junctional nodes could be assessed during surgery to decide whether or not to proceed to D2 dissection, if these nodes were involved. The rationale is based on the apparently high morbidity of D2 dissection in Western series, and they suggested that D2 dissection should be avoided if possible.

Kato et al. [42] address the issue of limited nodal dissection and describe the predictive value of the number of metastatic nodes in the Japanese (old and new classifications) "n1" perigastric stations. They found their system to have higher sensitivity, specificity, and accuracy than the TNM system or the Japanese system.

Finally, Yu et al. [43] have proposed a frequency system, based on the ratio of metastatic to dissected regional lymph nodes (more or less than 25% involved). Such a system weights against limited nodal dissection, and is a relevant approach, assuming extended lymphadenectomy has an independent survival impact.

Conclusion

Despite repeated comparisons between Japanese and Western staging systems, the systems do not, and were not designed to, fulfill the same role. The JGCA classification is a comprehensive guide to the anatomical-based treatment of gastric cancer and its regional metastases. The staging system within the JGCA classification is highly detailed and anatomically based, and it is inseparable from the guidance on surgical treatment, which is its primary focus.

The TNM system is primarily used as a guide to prognosis. It contains no treatment guidance and has recently changed to a number-based N stage, which most accurately reflects metastatic burden and, hence, prognosis. It provides a simple and reliable means of comparison of outcome between series. In Western practice, importance is placed on both surgeon and pathologist to ensure a nodal yield of at least 15 nodes. The value of the number-based nodal system for comparison will be lost if node yields are low, as a consequence of stage migration, and comparison between patients classified by the TNM and Japanese systems will remain inadequate, as the Japanese approach of D2 dissection and specimen preparation invariably results in greater node yields.

As the two systems are different in principle, it is important that clinicians involved in the treatment of gastric cancer understand the roles of each system. Surgeons using the Japanese system are able to report results by both the Japanese and the TNM staging, which will help comparisons of outcome. However, the two systems are not interchangeable, and the systems and their terminology should not be mixed if clarity is to be maintained.

Alternative staging systems continue to be proposed. Most adapt either anatomical or number-based systems, confirming the independent value of each approach.

Acknowledgments The authors are grateful for the financial support of the Japanese Foundation for Pro-

motion of Cancer Research and the British Council. Special thanks to Mrs. Mitsuho Nakagawa for her secretarial work and assistance.

References

1. Davis P, Sano T. The difference in gastric cancer between Japan, USA and Europe: what are the facts? What are the suggestions? Crit Rev Oncol Hematol 2001;40:77–94.
2. Sobin LH, Wittekind Ch, editors. TNM classification of malignant tumors. 6th Ed. New York: Wiley-Liss; 2002.
3. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 2nd English edition. Gastric Cancer 1998;1:10–24.
4. Kennedy BJ. TNM classification for stomach cancer. Cancer 1970;26:971–983.
5. Hermanek P, Henson DE, Hutter RVP, Sobin LH, editors. TNM supplement 1993: a commentary on uniform use. Berlin Heidelberg New York Tokyo: Springer; 1993.
6. Okusa T, Nakane Y, Boku T, Takada H, Yamamura M, Hioki K, et al. Quantitative analysis of nodal involvement with respect to survival rate after curative gastrectomy for carcinoma. Surg Gynecol Obstet 1990;170:488–94.
7. Ichikura T, Tomimatsu S, Okusa Y, Uefuji K, Tamakuma S. Comparison of the prognostic significance between the number of metastatic lymph nodes and nodal stage based on their location in patients with gastric cancer. J Clin Oncol 1993;11:1894–900.
8. Roder JD, Bottcher K, Busch R, Wittekind C, Hermanek P, Siewert JR. Classification of regional lymph node metastasis from gastric carcinoma. German Gastric Cancer Study Group. Cancer 1998;15;82:621–31.
9. Mok YJ. Summary of the 12th International Seminar and 6th General Meeting of the WHO Collaborating Centre for Gastric Cancer. IGCA News 1997;3:6–8.
10. Japanese Research Society for Gastric Cancer. The general rules for the gastric cancer study in surgery. Jpn J Surg 1973;3:61–71.
11. Kajitani T. The general rules for the gastric cancer study in surgery and pathology. Part I. Clinical classification. Jpn J Surg 1981;11:127–39.
12. Japanese Research Society for Gastric Cancer. Japanese classification of gastric carcinoma. First English Ed. Tokyo: Kanehara; 1995.
13. Aiko T, Sasako M. The new Japanese Classification of Gastric Carcinoma: points to be revised. Gastric Cancer 1998;1:25–30.
14. Sasako M, McCulloch P, Kinoshita T, Maruyama K. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. Br J Surg 1995;82:346–51.
15. Moynihan BGA. The surgical treatment of cancer of the sigmoid flexure and rectum. Surg Gynecol Obstet 1908;6:463–6.
16. Gervasoni JE Jr, Taneja C, Chung MA, Cady B. Biologic and clinical significance of lymphadenectomy. Surg Clin North Am 2000;80:1631–73.
17. Roviello F, Marrelli D, Morgagni P, de Manzoni G, Di Leo A, Vindigni C, et al. Italian Research Group for Gastric Cancer. Survival benefit of extended D2 lymphadenectomy in gastric cancer with involvement of second level lymph nodes: a longitudinal multicenter study. Ann Surg Oncol 2002;9:894–900.
18. Fuji K, Isozaki H, Okajima K, Nomura E, Niki M, Sako S, et al. Clinical evaluation of lymph node metastasis in gastric cancer defined by the fifth edition of the TNM classification in comparison with the Japanese system. Br J Surg 1999;86:685–9.
19. Ichikura T, Tomimatsu S, Uefuji K, Kimura M, Uchida T, Morita D, et al. Evaluation of the new American Joint Committee on Cancer/International Union Against Cancer classification of lymph node metastasis from gastric carcinoma in comparison with the Japanese classification. Cancer 1999;86:553–8.
20. Hayashi H, Ochiai T, Suzuki T, Shimada H, Hori S, Takeda A, et al. Superiority of a new UICC-TNM staging system for gastric carcinoma. Surgery 2000;127:129–35.
21. Ichikawa D, Kurioka H, Ueshima Y, Shirono K, Kan K, Shioaki Y, et al. Prognostic value of lymph node staging in gastric cancer. Hepatogastroenterology 2003;50:301–4.
22. Kodera Y, Yamamura Y, Shimizu Y, Torii A, Hirai T, Yasui K, et al. The number of metastatic lymph nodes: a promising prognostic determinant for gastric carcinoma in the latest edition of the TNM classification. J Am Coll Surg 1998;187:597–603.
23. Katai H, Yoshimura K, Maruyama K, Sasako M, Sano T. Evaluation of the new International Union Against Cancer TNM staging for gastric carcinoma. Cancer 2000;88:1796–800.
24. Karpeh MS, Leon L, Klimstra D, Brennan MF. Lymph node staging in gastric cancer: is location more important than number? An analysis of 1038 patients. Ann Surg 2000;232:362–71.
25. Kranenbarg EK, Hermans J, Van Krieken JHJM, Van de Velde CJH. Evaluation of the 5th edition of the TNM classification for gastric cancer: improved prognostic value. Br J Cancer 2001;84: 64–71.
26. Mendes de Almeida JC, Limbert M, Mendes de Almeida JM. Does the new classification (1997) improve prognostic stratification in gastric cancer submitted to R0 surgery? Eur J Surg Oncol 1999;25:280–3.
27. de Manzoni G, Verlato G, Guglielmi A, Laterza E, Tomezzoli A, Pelosi G, et al. Classification of lymph node metastases from carcinoma of the stomach: comparison of the old (1987) and new (1997) TNM systems. World J Surg 1999;23:664–9.
28. Lee WJ, Hong RL, Lai IR, Chen CN, Lee PH, Chung KC. Reappraisal of the new UICC staging system for gastric cancer: problem in lymph node stage. Hepatogastroenterology 2002;49: 860–4.
29. Bando E, Yonemura Y, Takeshita Y, Taniguchi K, Yasui T, Yoshimitsu Y, et al. Intraoperative lavage for cytological examination in 1297 patients with gastric carcinoma. Am J Surg 1999;178:256–62.
30. Bonenkamp JJ, Songun I, Hermans J, van de Velde CJ. Prognostic value of positive cytology findings from abdominal washings in patients with gastric cancer. Br J Surg 1996;83:672–4.
31. Bunt AM, Hermans J, van de Velde CJ, Sasako M, Hoefsloot FA, Fleuren G, et al. Lymph node retrieval in a randomized trial on Western-type versus Japanese-type surgery in gastric cancer. J Clin Oncol 1996;14:2289–94.
32. Siewert JR, Boettcher K, Roder JD, Busch R, Hermanek P, Meyer HJ. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. German Gastric Carcinoma Study Group. Br J Surg 1993;80:1015–8.
33. Bruno L, Nesi G, Montinaro F, Carassale G, Boddi V, Bechi P, et al. Clinicopathologic characteristics and outcome indicators in node-negative gastric cancer. J Surg Oncol 2000;74:30–2
34. Ichikura T, Ogawa T, Chochi K, Kawabata T, Sugasawa H, Mochizuki H. Minimum number of lymph nodes that should be examined for the Internatioanl Union Against Cancer/American Joint Committee on Cancer TNM classification of gastric carcinoma. World J Surg 2003;27:330–3.
35. Mullaney PJ, Wadley MS, Hyde C, Wyatt J, Lawrence G, Hallissey MT, et al. Appraisal of compliance with the UICC/AJCC staging system in the staging of gastric cancer. Union Internacional Contra la Cancrum/American Joint Committee on Cancer. Br J Surg 2002;89:1405–8.
36. Lee HK, Yang HK, Kim WH, Lee KU, Choe KJ, Kim JP. Influence of the number of lymph nodes examined on staging of gastric cancer. Br J Surg 2001;88:1408–12.
37. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading stastistics for survival in cancer. N Engl J Med 1985;312:1604–8.
38. Bunt AM, Hermans J, Smit VT, van de Velde CJ, Fleuren GJ, Bruijn JA. Surgical/pathologic-stage migration confounds com-

parisons of gastric cancer survival rates between Japan and Western countries. J Clin Oncol 1995;13:19–25.
39. de Manzoni G, Verlato G, Roviello F, Morgagni P, Di Leo A, Saragoni L, et al. The new TNM classification of lymph node metastasis minimises stage migration problems in gastric cancer patients. Br J Cancer 2002;87:171–4.
40. Adachi Y, Oshiro T, Okuyama T, Kamakura T, Mori M, Maehara Y, et al. A simple classification of lymph node level in gastric carcinoma. Am J Surg 1995;169:382–5.
41. Whiting JL, Hallissey MT, Rowlands DC, Fielding JW. Redefining surgery for gastric cancer. Gastric Cancer 1999;2:226–9.
42. Kato M, Saji S, Kawaguchi Y, Kunieda K, Sugiyama Y, Takagi Y, et al. A comparison of the prognostic significance between the number of metastatic lymph nodes and nodal stage in gastric carcinoma. Hepatogastroenterology 1999;46:3281–6.
43. Yu W, Choi GS, Whang I, Suh IS. Comparison of five systems for staging lymph node metastasis in gastric cancer. Br J Surg 1997;84: 1305–9.

Jpn J Clin Oncol 2004;34(8)481–488
doi:10.1093/jjco/hyh083

Meeting Report

Report of the Seventeenth International Symposium of the Foundation for Promotion of Cancer Research: Recent Advances in Gastric Cancer

John Whiting[1], Takeshi Sano[2], Mitsuru Sasako[2] and Jaffer A. Ajani[3]

[1]Department of Surgery, Queen Elizabeth Hospital, Birmingham, UK, [2]Gastric Surgery Division, National Cancer Center Hospital, Tokyo, Japan and [3]Department of Gastrointestinal Medical Oncology, University of Texas, M.D. Anderson Cancer Center, Texas, USA

Received June 23, 2004; accepted June 25, 2004

INTRODUCTION

The Seventeenth International Symposium of the Foundation for the Promotion of Cancer Research, "Recent Advances in Gastric Cancer", was held in Tokyo on March 15 to 17, 2004. The symposium was organized by Drs M. Sasako, J. Ajani, S. Hirohashi, A. Ohtsu, D. Saito, T. Sano and T. Ushijima with Dr T. Kakizoe as advisor.

WELCOME AND OPENING ADDRESS

Professor T. Sugimura [President Emeritus, National Cancer Center (NCC)] opened the Seventeenth International Symposium. Since 1987 over 500 speakers from around the world have been invited to discuss various cancers and this was the second symposium at which gastric cancer was discussed, the first being in 1998. Professor Sugimura stated his personal interest in this year's topic and recounted the history of his own gastric cancer, detected at screening and successfully treated at the NCC by total gastrectomy. Professor A. Ajani gave the opening address. Although there have been many successes in the diagnosis and treatment of gastric cancer there remain many unanswered questions. In epidemiology, environmental and genetic factors need to be identified and perhaps modified to reduce cancer rates. The differing incidences between the sexes and the geographical variation of sites of cancer occurence require explanation. Would it be possible to improve responses to chemotherapy and to target cancers with individualized therapy? These are major issues and this symposium offered a unique opportunity to discuss these dilemmas and challenges in detail.

For reprints and all correspondence: Takeshi Sano, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.
E-mail: tksano@ncc.go.jp

SESSION 1: EPIDEMIOLOGY, GENETICS AND PREVENTION OF GASTRIC CANCER

EPIDEMIOLOGY: CHAIRMAN PROFESSOR ADRIAN LEE

Professor P. Boyle [International Agency for Research on Cancer (IARC), Lyon, France] delivered the first presentation. Gastric cancer remains the second most common cause of cancer death in men and the fifth in women. There are large variations in incidence worldwide, rates being particularly high in the Far East and Eastern Europe. Etiological factors include smoking, salt intake, and incidence of *Helicobacter pylori*. Early studies of *H.pylori* underestimated its prevalence and more recent evidence suggests an odds ratio of at least 6.0 for the development of gastric cancer, an association exceeded only by that of cigarettes and lung cancer. Since the 1950s most countries have seen the incidence of gastric cancer halved. In the West this reduction has made the largest single contribution to the overall reduction in cancer mortality. Even now the exact reasons for this decline are not clear.

Trends in the incidence of gastric cancer in Japan were presented by Dr M. Inoue (NCC, Tokyo). Although lung cancer has recently become the leading cause of cancer related death, gastric cancer continues to be more common. The age-standardized incidence in Japan has fallen dramatically while the rapid ageing of the Japanese population has resulted in an increase in the absolute number of cases, increasing until 1995 before leveling off. The proportion of early disease increased from 25% in the 1970s to over 50% now. It is predicted that both age-standardized incidence and death rates will decline but that total cases will remain static and that the proportion of patients over the age of 80 will increase from 16% to nearly 40%. This will present many challenges for the future.

The incidence of tumors of the gastro-esophageal junction (GEJ) is thought to be increasing. Dr P. Hainaut (IARC, Lyon, France) addressed this issue. Carcinomas of the lower

esophagus (Siewert Type I) and those of the GEJ (Siewert Type II) are thought by many physicians to be synonymous. That they are different is witnessed by specific patterns of cytokeratin staining, differing expression of p53 mutation and the lack of Barrett's esophagitis in the type II tumors. Non-acid-secreting cardiac type mucosa is frequently seen at the GEJ and to many it represents a metaplastic change. In embryos however this cardiac mucosa is universal, marking it as a constitutive entity. After re-examining data on type I and II tumors and correcting misclassifications, the incidence of GEJ tumors has remained constant although there is little doubt that the incidence of adenocarcinomas of the lower esophagus is increasing rapidly.

Genetics: Chairman Professor Christian Wittekind

The Lauren intestinal and diffuse types of gastric cancer differ and Dr T. Ushijima (NCC Research Institute, Tokyo) summarized many of the genetic differences. Oncogene activation (β-catenin, K-ras and c-erbB2) and p53 mutations are frequent in intestinal type tumors (40%) compared with diffuse types (15%), but the greatest difference is in e-cadherin mutations, present in up to 50% of diffuse tumors but rare in the intestinal type. As well as direct genetic mutations, epigenetic inactivation of genes occurs and methylation of DNA, especially of promoter areas, is frequently a mechanism that prevents gene transcription. Methylated DNA is preserved after DNA replication preventing gene expression in daughter cells. Nine genes were identified as frequently methylated in gastric cancer cell lines and four were confirmed as methylated in tumors. One of these genes Lysyl Oxidase (LOX) has since been identified as a new tumor suppressor gene, suppressing the growth of tumors in LOX transfected nude mice.

Hereditary diffuse gastric cancer (HDGC) caused by germline e-cadherin mutations was first described in 1998 by Dr P. Guilford (University of Otago, Dunedin, New Zealand) who updated the symposium on its current status. Forty-four differing mutations have been identified worldwide with a penetrence of 80% in males and 70% in females. Within resected stomachs there are multiple signet ring micro-cancers (range 8–>300) with a predisposition for the transition zone between the body and antrum. There are no reports of prophylactic gastrectomy where tumor has not been found, indicating that these micro-cancers are potentially very slow growing and require a "second hit" to initiate invasion. Micro array gene mapping has identified c-src gene activation as one potential second hit. From a practical viewpoint endoscopy has previously missed many cancers but the use of Congo red dye spray has increased sensitivity such that endoscopy can be considered reliable.

Genetic alterations such as p53, β-catenin and e-cadherin are frequent in gastric carcinogenesis and the ability of gene micro array experiments to analyze thousands of genes has allowed classification of tumors at the molecular level as well as having identified novel molecular targets for therapeutics and diagnostics. Professor H. Aburatani (University of Tokyo) compared cancerous gastric and non-cancerous gastric tissue by micro array and identified genes associated with lymph node metastasis (Oct 2) or with type of tumor (LI cadherin). To assist with the interpretation of the vast amount of data produced (up to 51 000 genes) a new visualization tool, an "expression imbalance map" has been developed to allow differing gene expression to be visualized easily.

Prevention: Chairman Dr Jae-Moon Bae

High salt intake is a risk factor for gastric cancer. Dr S. Tsugane (NCC, Tokyo) presented two studies examining this relationship. The Eco cancer study selected 633 people aged 40 to 49 years from five geographical areas with large differences in gastric cancer mortality. There was a good correlation between salt intake and gastric cancer. A cohort study examined 100 000

people aged 40 to 69 years and again there was a good correlation between amount of salt consumed and subsequent development of cancer. A similar cohort study demonstrated a trend for reduced gastric cancer rates in people with higher consumption of fruit and vegetables. An RCT of vitamin C supplementation involving 439 randomized subjects demonstrated increased vitamin C plasma levels and a smaller change in pepsinogen I/II ratio (a surrogate maker for progression to atrophic gastritis) in the high dose group. Based on these results, reduction in salt intake and encouragement of consumption of fresh fruits and vegetables have the potential to reduce the risk of gastric cancer in Japan.

SESSION 2: *HELICOBACTER PYLORI* AND PATHOLOGY OF GASTRIC CANCER

HELICOBACTER PYLORI: CHAIRMAN DR PIERRE HAINAUT

Professor A. Lee (University of New South Wales, Sydney, Australia) presented evidence for *H.pylori* as a carcinogen. The Correa hypothesis of gastric carcinogenesis through gastritis, atrophy, intestinal metaplasia and dysplasia is widely accepted. *H.pylori* has been shown to be a potent initiator of inflammation and is classed as a carcinogen by the World Health Organization (WHO) although with an odds ration of only 1.92 many remain skeptical. Atrophy and intestinal metaplasia represent a hostile environment for *H.pylori* and early studies underestimated the extent of past infection. More recent studies suggest much higher ORs of up to 23. The location of gastritis is thought to determine the outcome of the disease with antral disease predisposing to duodenal ulcer and pangastritis predisposing to gastric ulcers or cancer. *H.pylori* cannot survive in the most acid producing areas of the stomach thriving only within a restricted pH range, most frequently found at the transition zone between body and antrum. In animal models as well as in humans reduction in pH with PPI, vagotomy or atrophy allows *H.pylori* to migrate proximally. There is mounting evidence that *H.pylori* strains that produce cagA, vacA or IL1B, as well as promoting carcinogenesis by inflammation, also have direct mitogenic effects on host cells.

In Mongolian gerbils (MGs) *H.pylori* infection results in chronic gastritis, peptic ulcers and intestinal metaplasia. Dr M. Tatematsu (Aichi Cancer Center Research Institute) updated the symposium on the status of these animal models. *H.pylori* infection and treatment of the stomach with N-nitroso compounds results in gastric cancers with an intestinal appearance. High salt diets acted synergistically. The duration of infection with *H.pylori* correlated with the risk of cancer, infection early in life enhancing it while eradication reduces the risk. There is some disagreement with the literature regarding *H.pylori* as a promoter or initiator of carcinogenesis, Dr Tatematsu's group finding *H.pylori* infection alone, insufficient for carcinogenesis. Experiments using chimeric mice demonstrate that each gastric gland has a single progenitor cell and that cancers are likewise clonal. The submucosal tumor-like lesions reported by others as induced by *H.pylori* are not clonal suggesting these are regenerative phenomena and that *H.pylori* acts only as a promoter of carcinogenesis.

The role of *H.pylori* eradication in reducing cancer risk remains controversial. Dr N. Uemura (International Medical Center of Japan, Tokyo) presented a follow-up study of 1526 endoscopy patients. No gastric cancers developed in the *H.pylori*-negative group ($n = 280$) but 2.9% of the *H.pylori*-positive group (36/1246) developed cancers. To investigate the role of *H.pylori* eradication, 132 patients with early gastric cancers (EGC) treated by endoscopic mucosal resection (EMR) had either *H.pylori* eradication ($n = 65$) or no eradication ($n = 67$). 16% ($n = 11$) or the non-eradicated group developed further cancers compared with 3% ($n = 2$) in the eradicated group ($P = 0.04$). Intragastric pH in the eradicated group reduced from a mean of 6 to 3. A cohort study from China supports these findings. 1630 *H.pylori*-positive patients, half with dysplasia ($n = 824$), were randomized to *H.pylori* eradication ($n = 820$) or not ($n = 810$). In the patients without initial dyplasia 1.5% (6/391) patients in the control group developed cancer versus 0% (0/413) in the eradicated group. For patients with initial dysplasia the figures were 1.5% (6/391) and 1.7%(7/407), respectively.

Having seen some evidence for the benefits of *H.pylori* eradication, Dr D.Saito (NCC, Tokyo) discussed some outstanding questions. Worldwide it is estimated that at least 60 million people are infected with *H.pylori* yet the incidence rate for gastric cancer among them is only 0.4%. Many countries with high infection rates have low cancer rates. Host and environmental factors are important but which is most important is unclear. There are also potential adverse effects of *H.pylori* eradication related to the recovery of gastric acid secretion with acute gastro esophageal erosions and gastro esophageal reflux disease (GERD) more prominent. GERD can predispose to Barrett's metaplasia a potentially premalignant lesion. There are published studies of *H.pylori* eradication and of these a Chinese and a South American study report benefit whilst an American Study did not. An intervention study in Japan has randomized 342 patients to eradication and 340 as a control group. End points are development and progression to mucosal atrophy and the trial is due to report in March 2004. Until the reports of this and other larger scale trials are known eradication cannot be recommended to all *H.pylori*-positive patients.

PATHOLOGY: CHAIRMAN PROFESSOR CORNELIS JH VAN DE VELDE

There are differences in the histological classifications used in the West and in Japan and Dr T. Shimoda (NCC, Tokyo) discussed the difficulties that arise in the diagnosis and differentiation of intramucosal carcinoma and dysplasia. In Japan the diagnosis of intramucosal carcinoma is based on structural features and cellular and nuclear atypia and invasion is not required. This has led to Western pathologists diagnosing cases

as low grade dysplasia that under Japanese classification were definite carcinomas. The Vienna classification allows five categories from 1 (negative for carcinoma) to 5 (invasive carcinoma). Category 4 (non-invasive high-grade dysplasia) includes as subgroups: high-grade adenoma, non-invasive carcinoma (carcinoma *in situ*) and suspicion of invasive carcinoma. Using this classification disagreements between Western and Japanese pathologists were limited to categories 4 and 5, both of which require treatment.

The most commonly used classifications for gastric cancer are the WHO, UICC and JGCA systems. Professor C. Wittekind (University Klinikum Leipzig, Germany) presented the differences and also the latest UICC classification. The WHO classification is based on the predominant histological subtype. Although reproducible, it suffers as most tumors are heterogeneous and it has limited prognostic value. The UICC and JGCA both stage tumors according to a TNM system and have very similar T and M stages. In the N classification, the UICC adopts a numerical system based on the number of involved nodes and the JGCA use an anatomical classification based on the site of involved lymph nodes relative to the tumor. The UICC state that: to allow accurate classification the minimum number of lymph nodes retrieved should be 16 but in cases where fewer nodes are found, so long as they are all negative, the tumor should be staged as N0 not Nx. Most parties agree that the UICC system is more accurate in determining prognosis but there are concerns that it offers no guidance to surgeons as to the extent of the required lymphadenectomy.

Dr H. Katai (NCC, Tokyo) presented the results of examining 4524 patients treated at the NCC between 1969 and 1990 for potential prognostic factors. Overall survival was 70.1% ranging from 13.7% for stage IV to 92.3% for 1A. Factors that were found to be significant include (Hazard ratio and 95% CI interval): D1 dissection (1.95; 1.69–2.25); Depth (1.31; 1.26–1.36); male sex (1.21; 1.08–1.35); older age (1.03; 1.02 −1.037); type IV macroscopic type (2.13; 1.76–2.58). Hazard ratios for N stage by JGCA were: for N1 1.39 (1.18–1.62); N2 2.58 (2.22–3.00) and N3 5.18 (4.28–6.27). The Hazard ratios for N stage by UICC were similar although the UICC had better discriminating power between pN1 and pN2 and poorer discrimination between pN2 and pN3. The importance of complete examination of lymph nodes was also demonstrated as there was downward stage migration in 14.9% of cases if nodes of 5 mm or less were ignored and 1.5% if nodes of 2 mm or less were ignored.

SESSION 3: SCREENING AND DIAGNOSIS OF GASTRIC CANCER

SCREENING: CHAIRMAN DR PARRY GUILFORD

Professor I. Tsuji (Tohoku University Graduate School of Medicine, Sendai) started the session with a report on screening in Japan. In 2001, 5.3 million people underwent mass screening representing 20% of the target population of all people aged 40 years or over. Each of the seven standard barium views of the stomach were reviewed by two radiologists. Sensitivity and specificity has been estimated at 70–90% and 80–90%, respectively, with a positive predictive value of 0.8–2.3%. Of those screened 10.3% were referred for endoscopy and 5275 cases of gastric cancer were diagnosed. Although the efficacy of mass screening has never been confirmed in randomized controlled trials, several observational studies demonstrate benefit. Three case–control studies show a pooled odds ratio of 0.39 (95%CI 0.29–0.52) for mortality in men from gastric cancer in the screened group and a ratio of 0.50 (0.34–0.72) for women. The reduction in mortality is attributable to the higher proportion of early gastric cancers in the screened group. Recent developments in screening revolve around changes in pepsinogen I/II ratios, measurable in a simple blood test, which are predictive of atrophic gastritis, a precursor of gastric cancer. Accuracy of this test is similar to that of contrast screening, but further proving trials are required before it can be considered for implementation.

Dr Jae-Moon Bae (NCC, Seoul, Korea) presented the rapid development of the national screening program in Korea. The program is targeted at lower income groups; those patients on Medicaid and beneficiaries of the National Health Insurance Corporation (NHIC). Screening is offered biannually to persons over the age of 40 years. As an incentive, the screening program qualified people for a 20% reduction in HNIC premiums, despite this the group's screening rate was 57.4% compared with 107.4% in the Medicaid group. In 2002, 806 699 people were screened using either double contrast barium meal or endoscopy, dependent on patient preference. The detection rate for gastric cancer was 0.11% in the Medicaid group and 0.13% in the NHIC group. The screening program was limited by a budget that, at $30.5 million, equated to $21 900 to detect each case of gastric cancer and a remarkable $38 to screen each person. The population in Korea aged over 40 years is 17 million and a randomized controlled trial of the effectiveness of the screening program was suggested before extending the screening program further.

DIAGNOSIS: CHAIRMAN PROFESSOR PETER BOYLE

Dr M. Kida (Kitasato University East Hospital, Sagamihara) presented recent developments in endoscopic ultrasound (EUS). EUS is 91.3% accurate for the diagnosis of intramural cancer but suffers in the diagnosis of submucosal (sm) cancer (67.7%) and invasion of the deeper muscle layers (65.7%). This is of crucial importance as new Japanese guidelines allow tumors with no likelihood of metastasis to be treated by endoscopic mucosal resection. These cancers are well-differentiated, intramural cancers and well-differentiated tumors less than 3 cm diameter with sm invasion <500 μm. A new development, three-dimensional EUS (3D-EUS) promises to improve accuracy significantly. In 3D-EUS a small scanning

head rotates as the head is automatically withdrawn within a sheath. The operator can set the speed of rotation and withdrawal and the resulting spiral image is akin to a spiral CT scan. Data can be manipulated to allow reconstruction in various planes including linear images and radial series. Accuracy is estimated at 5–10% higher than conventional EUS and importantly, for lesions larger than 0.5 cm diameter, depth of sm invasion can be determined with 75–100% accuracy.

Another new technology was presented by Dr G. Iinuma (NCC, Japan). Modern multi-detector row CT (MDCT) scanners perform highly detailed scans within a single breath hold. Computer manipulation of MDCT data allows the display of virtual endoluminal images (VEIs), views familiar to any endoscopist, as well as 3D reconstructions of the stomach. In 2003, 86 gastric cancers in 84 patients were assessed using VEIs and 3D views and compared with conventional diagnostic and staging data. Of the early lesions VEIs revealed 21/44 (47.7%) and 3D reconstructions 18/44 (59.5%). For advanced lesions 25/42 (59.5%) were identified on VEIs and 32/42 (76.2%) by 3D reconstruction. Whilst accuracy is presently insufficient for clinical use, the development of CT scanners with 16 scanning arrays compared with the current four, will lead to great improvements in resolution and the potential to revolutionize diagnosis and staging of gastric cancer.

Positive cytology of peritoneal washes is a poor prognostic indicator equating to M1 (cy1). However peritoneal recurrences occur in patients with negative cytology. To explain these recurrences Dr Y. Kodera (Nagoya University Graduate School of Medicine) reported the results of reverse transcriptase polymerase chain reaction (RT-PCR) with CEA as the target using a real time, Light Cycler instrument to detect and quantify CEA mRNA. Positive results were strongly predictive of peritoneal recurrence (83%) but this technique was unreliable in primary tumors not expressing CEA. To improve this accuracy RT-PCR against cytokeratin 20 (CK20) was performed in 195 patients but results were disappointing with accuracy of just 54% in predicting peritoneal recurrence. CEA RT-PCR remains the most sensitive method for predicting free cancer cells in the peritoneal cavity.

The effect of isolated tumor cells (ITC) detectable only by immunohistochemistry (IHC) or RT-PCR in lymph nodes has caused considerable controversy. They are frequently detected even in pT1A tumors (12–18%) and several papers report poorer prognosis when present. Dr M. Sasako (NCC, Tokyo) presented definitive data dismissing their importance. 402 patients from four centers with pT2pN0 (n = 221) and pT2pN1 (n = 181) tumors underwent D2 or greater surgery. ITC was detected by IHC in 187 cases, 81 (37%) of the pT2pN0 group and 106 (58%) of the pT2pN1 group. For ITC(−) the 5-year survival rate was 84.4% and 10-year survival 70.4%, for ITC(+) the rates were 83.9% and 72.9% (NS). For the pT2pN0 subgroup rates were 90.7% and 76.6% for ITC(−) and 91.4% and 78.2% for ITC(+) (NS). There were no significant differences between any of the survival curves and in multivariate analysis ITC was not an independent prognostic factor.

SESSION 4: SURGERY AND ADJUVANT THERAPY FOR GASTRIC CANCER

SURGERY 1 AND 2: CHAIRMEN PROFESSOR JAFFER A. AJANI AND DR ALAN ANTHONEY

The extent of lymph node dissection during gastrectomy continues to cause controversy with high mortality and lack of efficacy reported by the Dutch and British MRC randomized controlled trials (RCTs). Interim analysis of two D1/D2 and the final report on the Dutch RCT trials were reported.

Dr M. Degiuli (Division of Surgery, Turin, Italy) presented convincing evidence that D2 gastrectomy can be performed safely in the West. The Italian Gastric Cancer Study Group (IGCSG) RCT of D1 versus D2 resection involves five centers and has recruited 203 patients (97 D1 and 106 D2). To avoid excess mortality the protocol forbids distal pancreatectecomy and splenectomy unless there is direct organ invasion. Recruitment is ongoing. Morbidity is low at 4.1% in the D1 group and 6.6% in the D2 group. Only 3/203 (1.45%) patients have died, one from the D1 group and two after D2. There is a high proportion of T1 tumors (33%) and as these are less likely to have lymph node metastasis, there was some suggestion that this may cause the trial to be underpowered.

In Taiwan an RCT of D1 versus D2 has completed recruiting. Uniquely this trial with 110 D1 and 111 D2 cases was performed in one center by three surgeons allowing excellent surgical quality control with no post-operative mortality. Morbidity was higher in the D2 group (17.1% versus 7.3%), the difference largely attributable to intra-abdominal abscess formation (8.1% versus 0%) and minor anastamotic leak (4.5% versus 0%). Professor C.W. Wu (National Yang-Ming University, Taipei, Taiwan) presented the interim survival analysis. At a median follow-up of over 5 years there appeared to be a small survival advantage for the D2 group. After correcting for confounding factors that biased the results against the D2 group, 5-year survival was stated to be 15% better in the D2 group. The trial is due to complete when all patients have completed 5-year follow-up.

Professor C.J.H. van de Velde (Leiden University Medical Center, Netherlands) discussed the long term results of the Dutch RCT of D1 versus D2 trial. Follow-up is now available to 11 years and survival remains the same in both groups (31% versus 35% NS). The excess surgical mortality and morbidity in the D2 group was largely attributable to the distal pancreatectomy (DP) and splenectomy (S) but what is frequently not realized is the contribution that these procedures make to ongoing mortality, biasing results against the D2 group. In subgroup analysis excluding patients with DP and S, the higher mortality still seen in the D2 group is not significant (3.8% versus 6.3%) and survival differences at 5 (47% versus 56%) and 10 years (33% versus 47%) were significantly better in the

D2 group. Even though numbers are small the benefit of D2 gastrectomy was largely in patients staged as N2 by the new UICC staging system.

Three large RCTs have been organized by the Japanese Clinical Oncology Group (JCOG) examining the extent of surgery required in the treatment of gastric cancer and Dr T. Sano (NCC, Tokyo) appraised these trials. JCOG 9501 recruited 523 patients to a trial of D2+ para-aortic lymphadenectomy versus D2 for T2b/T3/T4 tumors. Morbidity was higher in the group undergoing more extensive surgery (29% versus 21%) but mortality was identical with only two deaths in each group. The final analysis is due in 2006. The current trial (JCOG 0110) commenced in 2002 and will recruit 500 patients with T2 or greater proximal cancers. Randomization will be between splenectomy and spleen preservation. Although splenectomy is performed without increased mortality in Japan JCOG 0110 will compare reduction in morbidity associated with spleen preservation against the risk of local recurrence. JCOG 9502 was a trial comparing abdominal (A) approach versus thoracoabdominal (TA) approach with dissection of some mediastinal nodes for gastric cancer with esophageal invasion. The TA approach was expected to prove superior. After 8 years the first interim analysis was performed on 165 patients. There was only one death in the TA group but morbidity was significantly higher (47% versus 34%). Survival was better at all times in the A group (NS). The estimate for the possibility of a significant survival advantage occurring in the TA group if the trial was completed was 3.65% and the trial was halted.

Following trials the discussion turned to surgical techniques. In 2001 in Japan 959 cases of laparoscopy assisted distal gastrectomy (LADG) were performed, up from just 59 in 1996. Professor S. Kitano (Oita University) presented his department's results with LADG. The technique involves a laparoscopic dissection including D1 + α and mobilization of the stomach. Division of the stomach and reconstruction are then performed via a mini laparotomy. Of 136 patients treated mean operating time was 238 minutes with 7% morbidity. Two non-gastric cancer deaths occurred and there has been no recurrent disease. Professor Kitano suggested that for an individual experienced in both open gastric surgery and laparoscopic surgery the learning curve would be relatively short, about 10 cases.

Continuing the theme of less extensive surgery, Dr Y. Kitagawa (Keio University School of Medicine) talked on sentinel node biopsy and its applications in gastric cancer. In a proving study with 270 patients with T1/2 N0 disease, 99 m-Technetium Tin colloid was injected endoscopically in to the tumor basin prior to conventional D2 gastrectomy. Sentinel nodes were detected using a hand held gamma probe and confirmation was by histology using routine H&E stain to detect the colloid. Frequently more than one sentinel node was found (average 4.1) and the detection rate for sentinel nodes was 97% with 99% accuracy. In 37% of cases sentinel nodes were found in JGCA N2 nodes. Laparoscopic wedge resection with confirmation of N0 status requires absolute accuracy from sentinel node mapping and the application of real time intraoperative RT-PCR is being investigated.

ADJUVANT THERAPY

CHAIRMAN: DR AL BENSON

The results of the South Western Oncology Group trial of adjuvant chemoradiotherapy (SWOG9008) have caused a re-examination of the role of adjuvant and neoadjuvant therapies in gastric cancer. Dr D. Ciot (Memorial Sloan-Kettering Cancer Center, New York, USA) and Professor C.J.H. van de Velde (Leiden University Medical Center, Netherlands) discussed the history of such treatments, the implications of SWOG9008 and future directions for trials.

Most prospective RCTs of adjuvant therapy have failed to demonstrate a benefit and have been criticized as being underpowered, using out dated treatments and having heterogeneous patient populations. Recent meta-analyses of these trials have suggested a small benefit in the order of 3–5%. SWOG9008 randomized 566 patients to either observation or postoperative 5-FU/leucovorin and 4500 cGy of fractionated radiotherapy. Improvements in median survival (27 versus 36 months) and 3-year survival (41% to 50%) were seen. Toxicity was a problem and despite the trial being limited to fit patients a third of the chemoradiotherapy arm were unable to complete treatment. The benefit of treatment appears to be largely related to improved locoregional control but both in this and in survival, the observation arm did particularly badly compared with patients in the Dutch D1/D2 trial, and the treatment arm had only comparable results with the Dutch group. This may be explained by the majority of cases having had inadequate clearance of even the N1 nodes (D0). Application of the Muruyama Index (MI) that rates the probability of lymph node metastasis based on the primary tumor's characteristics suggested considerable residual disease. Paradoxically in the subgroup where the probability of residual disease was low the beneficial effects of chemoradiotherapy appeared greater. Both surgeons concluded that although chemoradiation demonstrated benefit after poor surgery, the result could not be extrapolated to show benefit after surgery with a more radical lymph node clearance. Professor van de Velde outlined the proposal for a new Pan European Gastric Adjuvant Study with Uniform Surgery (PEGASUS), comparing adequate (D1 or greater with preservation of spleen and pancreas) surgery alone with adequate surgery with chemoradiotherapy.

The Japanese perspective on adjuvant therapy was given by Dr T. Kinoshita (NCC East, Tokyo). Two large RCTs of adjuvant treatment versus observation JCOG 8801 (MMC + 5-FU + oral UFT) with 579 patients and JCOG 9206 (MMC + 5-FU + CA + oral 5-FU) with 252 patients failed to demonstrate benefit. The results of JCOG 9206-2 with 282 patients comparing surgery + cisplatin + 5-FU + oral UFT with surgery alone are expected soon. S-1 is a new orally available agent with low toxicity and high single agent response rate. The

ACTS-GC trial (Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer) involving nearly 100 participating centers compares adjuvant S-1 with observation after surgery. The trial has recruited 800 of the target 1000 and will complete recruitment this year. Three phase II trials of neoadjuvant treatment are ongoing. Like his Western colleagues Dr Kinoshita's opinion was that SWOG9008 was not directly applicable to Japanese institutions where D2 lymph node dissections are routine.

SESSION 5: EMR AND MEDICAL ONCOLOGY

EMR: Chairman Professor Chew-Wun Wu

A recurrent problem for endoscopic mucosal resection (EMR) when dealing with lesions larger than 15 mm in diameter is the assessment of the depth of invasion where pre-treatment diagnosis is incorrect in 20% of cases. Conventional EMR techniques suffer from removing tumors piecemeal compromising pathological assessment in up to 30% and resulting in up to 17% local recurrence rate. En block resection suffers less from these problems and Dr T. Gotoda (NCC, Tokyo) demonstrated EMR with an "Insulated Tip" (IT) knife. Lesions up to 13 cm in diameter have been treated and of 2000 cases there has been only one local recurrence. The complication rate was 10% (7% bleeding and 3% perforation) and virtually all have been treated successfully endoscopically (the perforations with clips). Only 8 patients have required emergency surgery.

Medical Oncology: Chairmen Dr Maurizio Degiuli and Dr Daniel Coit

Professor J.A. Ajani (University of Texas MD Anderson Cancer Center, USA) began the session on the North American perspective with a brief overview of the current agents used worldwide. There are significant problems in evaluating treatments including a deficit of phase III trials and problems with trial methodology. Trials are now international and methodology and reporting should be standardized to allow conclusions to be universally applicable. Differences in treatments would continue as cultural differences on the acceptability of side effects varied. As examples he cited higher acceptance of hair loss in the USA and Europe compared to Japan and India and tolerance of higher doses of S-1 by Japanese compared to European patients. He stated his belief that current evidence favored newer agents such as CPT-111, S-1 and oxaliplatin over 5-FU and cisplatin.

Dr A. Ohtsu (NCC East, Tokyo) presented the results of JCOG 9205, a trial of 5-FU versus 5-FU and cisplatin versus UFT + mitomycin C in advanced cancer. Although 5-FU + cisplatin gave higher response (34%) rates than 5-FU alone (11%), there was no difference in survival and 5-FU remains the standard for control arms of new trials. A brief review of previous JCOG trials demonstrated slight survival benefits for chemotherapy compared with best supportive treatment. New agents are undergoing phase II trials and S-1 appears promising with a single agent response rate of 45%. Non-controlled audit data suggests that, since the approval of S-1 and Taxanes, 3-year survival rates have increased from 2% to 9%. S-1 and CPT-111 are currently undergoing phase III trials in advanced cancer. JCOG 9912 will recruit 450 patients and compares 5-FU versus cisplatin + CPT-111 versus S-1 with survival as the primary endpoint. 322 patients have accrued since October 2000. A post marketing RCT of S-1 versus S-1 + cisplatin has recruited 210 of the target 300. The final outcomes of both trials are expected in 2006.

Dr A. Anthoney (University of Leeds, UK) presented a brief history of trials within Europe. Over the last 15 years 5-FU has provided the mainstay of treatment in combination with other drugs. In a large British trial of ECF versus FAMTX, ECF was superior with a response rate of 40% and a median survival time of 9.4 months. In the UK ECF is mainly used to palliate symptoms, a role where high response rates and rapid response times are of clinical importance. In Italy phase II trials have shown superior response rates for the PELF regimen and this has become routine care in Italy. As elsewhere, new agents such as the taxanes, oxaliplatin and capecitabine are undergoing phase II trials but 5-FU and cisplatin remain the mainstays of treatment throughout Europe.

The final two presentations focused on the use of tests for chemosensitivity and individualized treatment. Dr T. Kubota (Keio University) summarized retrospective trial data on chemosensitivity suggesting that laboratory tests of a tumor's chemosensitivity could predict outcome. Prospective data on 128 patients with stage III and IV cancers undergoing surgery and chemotherapy, demonstrated 85% 3-year survival rates in sensitive versus 52% in insensitive patients. Gene array mapping of tumors have implicated COX2, VEGF, a putative potassium channel, retinoblastoma binding protein-1 isoform, thymidylate kinase and dihydropyrimidine dehydrogenase as genes important for chemosensitivity. Transfection of COX2 and VEGF into cell lines not natively expressing these genes, demonstrated that COX2 confers chemoresistance but VEGF did not. In mice however COX2 inhibitors were unable to increase sensitivity to chemotherapy.

Tumors are not homogeneous and Professor A. Benson III (Northwestern University's Feinberg School of Medicine, Chicago, USA) discussed targeting treatment based on molecular profiles and avoiding drugs where there was a high probability of resistance. The use of gene arrays was providing large numbers of potential molecular markers but before being used as predictive markers they must be demonstrated to have significant and independent value and be validated by clinical testing. The use of novel agents should also be explored. Examples include vaccination to gastrin 17, a growth promoter for a large number of tumors, where production of antibodies predicted a longer survival, and matrix metalloproteinase inhibitors, which appeared to offer benefits to patients post chemotherapy. In summary as well as new agents; new

targets, new markers, and new methods to establish response to treatment should all be investigated further.

CLOSING ADDRESS: CHAIRMAN PROFESSOR A. AJANI

Dr M. Sasako (NCC, Tokyo) gave the closing address where he thanked both speakers and attendants. The word encompassing the meeting was heterogeneity. Heterogeneity among cancers caused difficulties in staging and classification and with the epidemiology of the varying sites and types of tumor. Heterogeneity required tailoring surgery to the type and stage of cancer and to the patient. Most importantly heterogeneity between tumors and the identification of more homogeneous subgroups might allow individualized chemotherapy with the promise of better results. He called for a third meeting of this symposium in 6 years time to discuss further outcomes.

ELSEVIER

Surgical Oncology 13 (2004) 235–238

Surgical Oncology

www.elsevier.com/locate/suronc

Gastric cancer surgery in the elderly without operative mortality

Hitoshi Katai*, Mitsuru Sasako, Takeshi Sano, Takeo Fukagawa

Department of Surgical Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

Abstract

Background: Surgeons are increasingly being faced with the problem of treating elder gastric carcinoma patients. Recent improvements in the techniques for preoperative diagnosis and perioperative management have been made. The purpose of this study was to elucidate whether these improvements have produced a decrease in postoperative complications and mortality and resulted in a better clinical outcome.

Methods: Between 1993 and 2003, 141 elderly patients (aged 80 years or above) with gastric cancer underwent operation under the care of dedicated staff surgeons. The results of treatment were analysed.

Results: 52 (36.9%) patients had a diagnosis of gastric cancer during a health-check. Only 19 patients (13.5%) had no preoperative risk factors. The ASA score was II in 80%. Approximately 35% of the patients had early gastric cancer. Nodal metastasis was observed in 56% of the patients. The proportion of stage I patients was 40%.

Resection rate was 95.7%. Reduced nodal dissection (<D2) was common (47%). The surgery-related complication rate was as low as 8% and the number of operation-related deaths was zero. The 3 (5) year survival rates were 59.0 (48.2–69.8), 48.8 (36.0–61.6) % overall, and 70.0 (58.3–81.7), 56.6 (41.4–71.8) % after curative resection. The 3 (5) year survival rate was 80.3 (63.9–96.7), 73.6 (54.0–93.2) % for early gastric cancer.

Conclusions: Gastrectomy for elder patients can be carried out very safely by specialists with an excellent patient prognosis.

Keywords: Gastric carcinoma; The elderly

1. Introduction

The Japanese population is ageing. Life-expectancy is currently 78.36 years for men and 85.33 years for women [1]. Despite a decrease in the incidence of gastric carcinoma, the number of patients aged 80 years and older (elder patients) with this disease is increasing. We previously reported the outcome of 112 elderly gastric cancer patients treated between 1971 and 1990 and showed gastric cancer surgery in elderly patients without co-morbidities was safe [2]. Since then, improvements have been made with regard to socioeconomic conditions, medical progress for perioperative care and operative apparatus, and preventive medicine. The purpose of this study was to elucidate whether these improvements have produced a decrease in postoperative complications and mortality, and resulted in a better clinical outcome.

2. Patients and methods

Out of 4395 patients with gastric adenocarcinoma who underwent laparotomy under our care (5 dedicated staffs, specialists in gastric cancer) between 1993 and 2003, 141 patients (3.2%) were 80 years of age and older. Since 2001, we have recorded every patient with gastric carcinoma who has visited our hospital. One hundred and seventy-two elderly patients with gastric carcinoma visited our hospital between 2001 and 2003. Sixty patients (35%) were operated upon by us and other 112 patients (65%) were treated either by

*Corresponding author. Tel.: +81 3 3542 2511; fax: +81 3 3542 3815.

E-mail address: hkatai@ncc.go.jp (H. Katai).

0960-7404/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.suronc.2004.09.007

endoscopic mucosal resection for early gastric cancer or best-supportive care for advanced tumours.

Curative operations were our aim, even in the elderly patients. However, we did try to perform limited dissection and to avoid total gastrectomy as long as curability was preserved [2].

Surgical specimens were examined and scored according to the Japanese Classification of Gastric Carcinoma [3]. Medical records were reviewed for preoperative medical conditions, further histological, and follow-up data. The latest follow-up was July 24, 2004. The conclusive physical status of patients and their surgical risks were classified according to the American Society of Anesthesiology classification of physical status (ASA class I–V). Survival rate was calculated using the Kaplan-Meier method with 95% Confidence Limits (CL).

3. Results

3.1. Patients' characteristics

The median age was 83 years (80–94 years). There were 95 male and 46 female patients. Eighty-nine patients (63.1%) visited hospital with symptoms. However, 52 (36.9%) patients had a diagnosis of gastric cancer during a health-check. Twenty patients (14.2%) were treated for other cancers before the diagnosis of gastric cancer. Median Body Mass Index (BMI) was 21.4 (11.7–32.5) Kg/m^2: BMI <20 ($n=50$), $20 \leq$ BMI <24 ($n=62$), BMI ≥ 24 ($n=29$).

3.2. Preoperative morbidity (Table 1)

Table 1 Nineteen patients (13.5%) had no preoperative risk factors. Over 20% of the elderly patients had hypoalbuminaemia (<35g/l), and 16% had anaemia (haemoglobin <100 g/l). Electrocardiogram (ECG) abnormalities were detected in 55 patients (39.0%). Master's two-step exercise test was positive in 18 patients (12.8%). Abnormalities detected by echocardiography were mild in all cases. More than 35% of patients had abnormal respiratory function test. Fifty-seven patients (40.4%) had chronic diseases such as hypertension (22.7%), ischaemic heart disease (3.5%), and diabetes mellitus (9.9%). The ASA score was either II or III. in every patient.

3.3. Extent of tumour spread (Table 2)

Table 2 Approximately 35% of the patients had early gastric cancer. Nodal metastasis was observed in 56% of the patients. Distant metastasis was observed in liver up and peritoneum. We did not operate upon patients with

Table 1
Preoperative co-morbidities

	No. of patients	(%)
Hypoalbuminaemia Alb <35g/l	30	(21.3)
Anaemia Hgb <100 g/l	22	(15.6)
Abnormal heart evaluation		
ECG abnormalities	55	(39.0)
Master's two-step test-positive	18	(12.8)
Echocardiography		
Valve diseases	22	(15.6)
Low ejection fraction	3	(2.1)
Respiratory function test abnormal	53	(37.6)
Liver dysfunction	0	(0)
Creatinine clearance < 0.83 ml/s	21	(14.9)
Hypertension	32	(22.7)
Ischaemic heart disease	5	(3.5)
Abdominal aorta aneurysm	3	(2.1)
Diabetes Mellitus	14	(9.9)
ASA score = III	28	(19.9)

ASA, see text for definition.

Table 2
Extent of tumour spread

	No. of patients	(%)
Depth of tumour invasion		
T1	50	(35.5)
T2	28	(19.9)
T3	49	(34.8)
T4	14	(9.9)
Nodal involvement		
N0	62	(44.0)
N1	34	(24.1)
N2	33	(23.4)
N3	12	(8.5)
Peritoneal seeding		
P0	134	(95.0)
P1	7	(5.0)
Liver metastasis		
H0	137	(97.2)
H1	4	(2.8)
Other distant metastasis		
M0	141	(100)
M1	0	(0)
Lavage cytology		
CY0	125	(88.7)
CY1	16	(11.3)
Stages		
IA	44	(31.2)
IB	13	(9.2)
II	21	(14.9)
IIIA	20	(14.2)
IIIB	13	(9.2)
IV	30	(21.3)

Table 3
Surgical procedures

Type of operation	No. of patients	(%)
Total	44	(31.2)
Distal	81	(57.4)
Other resection	10	(7.1)
Bypass or exploration	6	(4.3)
Extent of dissection		
<D2	63	(46.7)
≥D2	72	(53.3)
Curability		
Curative resection (R0)	107	(75.9)
Non-curative resection (R≥1)	28	(19.9)
Bypass and exploration	6	(4.3)
ICU stay		
Elective	8	(5.7)
Emergency	1	(0.7)
No	132	(93.6)
Re-operation	2	(1.4)
Operation time (min)	194 (30–357) minutes	
Blood loss (ml)	310 (15–2572) ml	
Postoperative hospital stay (days)	17 (10–79) days	

Other resections includes surgical mucosectomy, wedge resection, and proximal gastrectomy.
Elective intensive care unit (ICU) stay was decided before the operation when the patients had severe co-morbidities.

other distant metastases. The predominant stage was stage I, followed by stages III, IV, and II.

3.4. Surgical procedures (Table 3)

Table 3 More than half of the patients underwent a distal gastrectomy. 53.3% of patients had resection with D2 lymph node dissection. Resection rate was 95.7% (135/141). One hundred and seven patients underwent operation with curative intent. The operation for the patients with positive lavage cytology was regarded as non-curative. The median operation time was 194 min Median blood loss was 310 ml. Postoperative hospital stay period was 17 days.

3.5. Early results (Table 4)

Table 4 Postoperative morbidity rate was 27.0% (38/141) overall, 28.0% (30/107) for the operations with curative intent, and 23.5% (8/34) for the palliative operations. There was no difference between curative and palliative operations. Surgery-related complications were less common. Pancreatic-related abscess was the most common. Pneumonia, regardless of the existence of aspiration, was most frequent postoperative complication. There was only one patient, who required intensive care unit (ICU) management due to postoperative complications.

Table 4
Postoperative complications

	No. of patients	(%)
Surgery-related		
Pancreatic-related abscess	10	(7.1)
Anastomotic leakage	1	(0.7)
Bleeding	0	(0)
Others	0	(0)
Non-surgery-related		
Pneumonia	13	(9.2)
Pulmonary embolism	0	(0)
Cardiac	5	(3.5)
Liver	2	(1.4)
Delirium	4	(2.8)
Empty disturbance	5	(3.5)
Others	2	(1.4)
Overall	38	(27.0)

The operation-related death was zero. The hospital mortality rate was also zero.

3.6. Survival

Fifty-nine patients died during the follow-up period. Forty-three of the deaths were related to gastric cancer. Twelve of the patients died of other causes (20.3%). Six were due to other malignancies (10.1%), six were due to other diseases (10.1%). Four occurred for unknown reasons (6.8%). Twenty-nine patients died within one year of their operation.

The 3-year survival rates were 59.0 (48.2–69.8)% for the whole population, 70.0 (58.3–81.7)% after curative resection and 16.1 (0–33.7)% after non-curative operations. After operations with curative intent, the 3-year survival rate was 80.3 (63.9–96.7)% for early gastric cancer, and 61.8 (45.7–77.9)% for advanced gastric cancer. The 5-year survival rates were 48.8 (36.0–61.6)% for the whole population, 56.6 (41.4–71.8)% after curative resection and 16.1 (0–33.7)% after non-curative operations. After operations with curative intent, the 5-year survival rate was 73.6 (54.0–93.2)% for early gastric cancer, and 41.7 (20.0–63.4)% for advanced gastric cancer.

4. Discussion

The Japanese population is ageing. However, they are still educated enough to be interested in health-checks for gastric cancer. A better public education of the elderly has increased cancer awareness, and thereby decreased the risk of developing symptoms, cases that are traditionally associated with a poor prognosis.

The increased age of the population is accompanied by an increase in age-related diseases. The preoperative surgical risk is often high, as has been reported in

Refs. [2,4,5]. However, the grade of complications were usually not severe in our series. Although we observed a high incidence of hypoalubuminaemia and low BMI, nutritional support via intravenous hyperalimentation was not essential before the operation. The ASA score was II in 80% and they did not have severe complications. They were only classified as score II because of their age i.e. 80 years and older.

The number of patients with stage I disease was 40% and less than that of previous study reported in Ref. [2]. Widespread use of endoscopic treatment has contributed to a decrease in gastrectomy for patients with early gastric cancer [6].

The resection rate of gastric carcinoma in the elderly has reached 95.7%, due to the early detection of disease and the ability to perform extensive resections, as well as the enormous improvements in preoperative staging.

Studies from other countries have reported high morbidity and mortality rates [4,5], especially in emergency cases. However, surgery-related complications were decreased in our study compared with those in previous series and the operation-related death rate was zero.

We previously reported that total gastrectomy and extended nodal dissection were both associated with a high operation-related death rate, especially in patients with preoperative morbidity. Therefore, curative operations were our aim, but at the same time, making efforts to perform limited dissections and to avoid total gastrectomy whilst preserving curability. The proportions of extended dissections was as low as 53% in our series.

There were very few obese patients in our series and these cases have higher morbidity and mortality rates [7]. In addition, the grade of preoperative co-morbidities was not severe in most of our patients. Our operations were all elective. In our institution, operation for gastric carcinoma is carried out only by specialists since 1993. Our stapling technique has improved and reduced the anastomotic leak rate [8]. Abscesses were common in the past after total gastrectomy with splenectomy. However, management of the abscess has been standardised as a result of a careful evaluation of past cases [9]. These factors have contributed to a decrease in our morbidity and mortality rates.

Gastrectomy can be carried out very safely in elderly patients by specialists. The survival rate was better than in the previous series. Life-expectancy for the general population of 80 years and older has increased and is now 8.26 years for males and 11.04 years for females. Therefore, death by other causes has decreased in this study. The 3(5)-year survival rate for early gastric cancer was excellent; 80.3 (73.6)%. Overall, 3(5)-year survival rates for the Japanese general population are 79 (61)%. There was no significant difference in survival between the early gastric cancer group and the general population.

Studies from the literature have reported that even patients with early gastric cancer usually die within 3 years without treatment [10]. Achievement of a curative R0 resection is always important, even for elderly patients.

Survival after non-curative resection is very poor. There is seldom an indication for a palliative distal or total gastrectomy. Preoperative staging, including laparoscopic exploration, is important to find candidates for surgical resection.

References

[1] Abridged life table for Japan. 2003. Tokyo: Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour, and Welfare, 2004.

[2] Katai H, Sasako M, Sano T, Maruayama K. The outcome of surgical treatment for gastric carcinoma in the elderly. Japanese Journal of Clinical Oncology 1998;28:112–5.

[3] Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma. Gastric Cancer 1998; 1: 10–24 (2nd English ed.).

[4] Houry S, Amenabar J, Rezvani A, Huguier M. Should patients over 80 years old be operated on for colorectal or gastric cancer? Hepato-gastroenterology 1994;41:521–5.

[5] Wu C-W, Lo S-S, Shen K-H, Hsieh M-C, Lui W-Y, P'eng F-K. Surgical mortality, survival, and quality of life after resection for gastric cancer in the elderly. World J Surg 2000;24:465–72.

[6] Nakajima T. Gastric cancer treatment guidelines in Japan. Gastric Cancer 2002;5:1–5.

[7] Inagawa S, Adachi S, Oda T, Kawamoto T, Koike N, Fukao K. Effect of fat volume on postoperative complications and survival rate after D2 dissection for gastric cancer. Gastric Cancer 2000;3:141–4.

[8] Nomura S, Sasako M, Katai H, Sano T, Maruyama K. Decreasing complication rates with stapled esophagojejunostomy following a learning curve. Gastric Cancer 2000;3:97–101.

[9] Sasako M, Katai H, Sano T, Maruyama K. Management of complications after gastrectomy with extended lymphadenectomy. Surgical Oncology 2000;9:31–4.

[10] Matsushita I, Hanai H, Kajimura M, Tamakoshi K, Nakajima T, Matsubayashi Y, et al. Should gastric cancer patients more than 80 years of age undergo surgery? Comparison with patients not treated surgically concerning prognosis and quality of life. Journal of Clinical Gastroenterology 2002;35:29–34.

Review Article

Digestive Diseases

Dig Dis 2004;22:338–344
DOI: 10.1159/000083596

Update on Surgery of Gastric Cancer: New Procedures versus Standard Technique

Hitoshi Katai Takeshi Sano Mitsuru Sasako Takeo Fukagawa Makoto Saka

Department of Surgical Oncology, National Cancer Center Hospital, Tokyo, Japan

Key Words
Gastric cancer · Early gastric cancer, surgery · Node dissection

Abstract
D2 lymphadenectomy has been the mainstay of treatment for every stage of gastric cancer including early gastric cancer in Japan. However, the use of conventional D2 nodal dissection is being challenged. There was a recent improvement in techniques for preoperative diagnosis and perioperative diagnosis. Less extensive surgeries to maintain patients' quality of life have been introduced as standard treatment for some forms of early gastric cancer in the Gastric Cancer Treatment Guidelines 2001 (The Japanese Gastric Cancer Association). Superextended dissection (more than D2) for non-early gastric cancer is set at investigational treatment. Japanese surgeons are now aiming at wide variations of surgical treatment according to the stage of disease based on new procedures. Further evaluations are proceeding to prove superior to standard techniques.

Introduction

D2 lymphadenectomy has been the mainstay of treatment for every stage of gastric cancer including early gastric cancer [1, 2]. However, the use of conventional D2 nodal dissection is being challenged, especially for early gastric cancer.

The Japanese Gastric Cancer Association issued the first version of Gastric Cancer Treatment Guidelines in March 2001 and a revised version appeared in 2004 [3]. The aim of this article is to introduce an outline of treatment guidelines for doctors' reference. The guidelines aim to provide a standard indication for doctors to select the proper treatments of gastric cancer according to the clinical stages of patients.

Although gastrectomy of at least two-thirds of the stomach with D2 node dissection was assigned as a standard treatment for most stages of advanced gastric cancer, modified surgeries were also described as standard or investigational treatments in the guidelines. Less extensive gastrectomy, which is widely performed in Japan at present for 'presumed mucosal cancers', is authorized. More extensive dissection (D3) is set at investigational treatment.

In this article we report the background of modified treatments and describe the details of every treatment.

Less Extensive Surgery for Early Gastric Cancer

Background

D2 lymphadenectomy and detailed histopathologic studies of the resected specimens have resulted in an accumulation of a vast amount of knowledge of the extent

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0257–2753/04/0224–0338$21.00/0

Accessible online at:
www.karger.com/ddi

Hitoshi Katai, MD
Department of Surgical Oncology
National Cancer Center Hospital
5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045 (Japan)
Tel. +81 3 3542 2511, Fax +81 3 3542 3815, E-Mail hkatai@ncc.go.jp