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Current Controversies in Cancer

Should Systematic Lymph Node Dissection be Recommended for Gastric Cancer?

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INTRODUCTION

THERE IS no doubt that systematic lymph node (LN) dissection is the most effective procedure to treat LN metastasis of gastric cancer. This surgical procedure has been developed in Japan over the last 30 years, and is now recognised as a standard and safe treatment. It has been improved by incorporating findings from many basic and clinical studies, i.e. anatomical and lymphographic studies, histopathological studies, statistical analysis of LN metastasis and prognosis, and also by progress in surgical techniques. To evaluate the Japanese style systematic LN dissection or D2 dissection, several multicentre trials have been conducted in European countries. Some reported excellent results supporting this surgical procedure. Other trials, however, have reported extremely high mortality and morbidity rates, and have concluded that ''LN dissection is not recommended for Western patients'' [16].

SCIENTIFIC BASIS OF LN DISSECTION

In 1936, Inoue published an important anatomical study on the lymphatic system around the stomach [1], which is the basis of systematic LN dissection. Deki and Sato completed a detailed and precise anatomical study of lymphatic channels in 1988 [2] and clearly demonstrated the lymphatic vessels and nodes which explain the routes of metastasis of gastric cancer. Sawai and co-workers demonstrated the lymphatic vessels and LNs in gastric cancer patients by injecting Indian ink into the submucosal layer of the stomach at pre-operative endoscopy [3]. Maruyama and colleagues studied the lymphatic system using an iodine contrast medium, Lipiodol emulsion, and found that the lymphaticus could be stained more clearly and easily by direct injection of contrast media into the perigastric LNs [4]. Takahashi's Indian ink was injected by this method, and the staining used as a guide to complete removal of the regional LNs.

The Japanese Research Society for Gastric Cancer published a manual in 1963, in which the regional LNs were classified into 16 stations (Figure 1). The classification has been improved by the afore-mentioned studies, and the latest English edition was published in 1995 [5]. The 16 LN stations are grouped as N1, N2, N3, and N4 according to the location and extension of the primary tumour. Complete removal of the N1 and N2 groups is called D2 lymphadenectomy or systematic LN dissection, and is considered to be the minimum requirement for gastric cancer surgery. Wider LN dissection is called D3 or D4 lymphadenectomy or extended LN dissection. When the N2 or N1 are not removed completely, the procedure is called D1 or D0 lymphadenectomy, i.e. conservative LN dissection.

Recently, Japanese and other specialists have considered that the extent of LN dissection should be planned according to the risk of metastasis at each LN station, and the effectiveness of LN dissection (i.e. the 5-year survival rate of patients with positive nodes). A computer information system was developed for this purpose and is in use in many centres worldwide [6].

Japanese surgeons have to optimise the extent and improve both the radicality and the safety of LN dissection, borrowing the philosophy underlying this procedure from several Western pioneers. McNeer and associates reported good treatment results after aggressive surgery [7], and their findings were very encouraging. Kajitani emphasised the effectiveness of systematic LN dissection [8], and Jinnai described the finer technical points of the procedure [9], called skeletonisation or complete exposure of all vessels and parenchyma of the neighbouring organs. McCulloch explained the Japanese

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Location and extension of tumour / Lymph node (LN) station	AMC MAC MCA CMA	A AM AD	M MA	MC	C CM
1 Right cardial LN		N2			
2 Left cardial LN	N1	N3 option	N2 option	N2	N1
3 LN along the lesser curvature					
4s LN along the left gastroepiploic a.		N1 option			
4d LN along the right gastroepiploic a.					N2 option
5 Suprapyloric LN			N1		
6 Infrapyloric LN					
7 LN along the left gastric a.			N2		
8a LN along the common hepatic a. (anterior)					
8p LN along the common hepatic a. (posterior)			N3		
9 LN around the celiac a.					
10 LN at the splenic hilum		N2 option		N2	
11 LN along the splenic a.					
12 LN in the hepatoduodenal ligament			N3		
13 LN in the post. surface of pancreatic head					
14a LN along the superior mesenteric a.	N4 option				
14v LN along the superior mesent. vein			N3		
15 LN along middle colic a.	N4 option				
16 LN around the abdominal aorta			N4		

Figure 1. Lymph node (LN) stations and classification N (compartment) in Japanese manual. The 16 core nodes are anatomically defined, nominated, and numbered. Furthermore, they are grouped into N1, N2, N3, and N4, according to the location and extension of the primary tumour. Principally, D2 lymphadenectomy is a complete removal of the N1 and N2 nodes (see p. 1480). However, several LN stations are treated as 'N1 option' or 'N2 option'. The D classification is not affected by excision or non-excision of these nodes [5]. A, distal third of the stomach; M, middle third; C, proximal third.

approach, including para-aortic LN dissection, very clearly in 1992 [10].

SURVIVAL BENEFIT OF LN DISSECTION

This treatment is not indicated for patients with distant metastasis, i.e. M1 patients. In the M0 patients, the 5-year survival rate following D2 lymphadenectomy was 63.8%, and was superior to survival after D1 or D0 lymphadenectomy (41.2% and 20.3%, respectively) in our series of 6537 patients (Figure 2). And systematic LN dissection showed a significantly better 5-year survival rate than non-systematic LN dissection in stage I, II, and III [11]. The major effect of systematic LN dissection is in the reduction of local recurrence. The proportion of local recurrences was decreased by the introduction of this procedure; 38% in 1967–1971, 12% in 1982–1986. According to a multivariate analysis of 2913 patients, the most important prognostic factor was the depth of tumour invasion, followed by LN metastasis and distant metastasis. It should be noted that the degree of LN dissection was the fourth most important prognostic factor [11].

Similar results have been reported by the Japanese Nationwide Registry of Gastric Cancer. These figures show that the overall 5-year survival rate after D2 gastrectomy was 63.8%, significantly higher than after D1 (41.2%) and D0 (20.3%) operations [12].

In the German multicentre trial, removal of 26 or more nodes was defined as radical LN dissection. From this trial, Siewert and colleagues reported that radical LN dissection prolonged survival, particularly for stages II and IIIa [13]. In stage II, the 5-year survival rates of radical and ordinary dissection were 55.2% and 26.8%, respectively, and they were 38.4% and 25.3% in stage IIIa. Brennan and Karpeh reported that the 5-year survival rate of N0 patients was no different between Japanese and American cancer centres, but was significantly different in N1 and N2 patients [14]. This difference in survival was attributed to the different techniques in the U.S.A. and Japan.

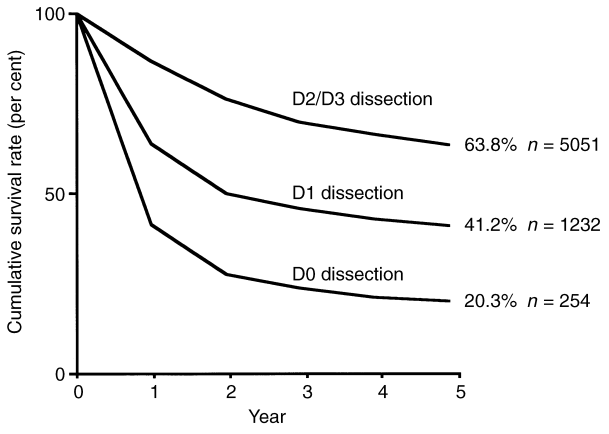

Figure 2. Survival rates by degree of lymphadenectomy. The D2/D3 lymphadenectomy group showed significantly better survival from the D1 and D0 groups. D2 lymphadenectomy had formerly been called R2 dissection until 1993. The letter R, however, is also used to describe residual tumour in the TNM classification. Therefore, in order to avoid such confusion, the Japanese Research Society for Gastric Cancer changed the letter from R to D to describe the degree of lymph node dissection [5]. National Cancer Center, Tokyo (1969–1991).

Table 1. *Mortality rate in several national trials*

Trial	Period	No. of hospitals	No. of patients	Mortality (%)
British [15]	1986–1993	32	400	9.3
Dutch [16]	1989–1993	80	996	8.1
German [13]	1986–1989	19	1654	5.1
Japanese registry [12]	1979–1982	141	20 064	1.7

Note that the aims were different in these trials. However, we can understand from the significantly different mortality rates that great differences exist among the trials, particularly in patient conditions, surgical procedures, and postoperative care.

Table 2. *Mortality and morbidity rates in the Dutch trial* (996 *patients treated at* 80 *member hospitals between* 1989 *and* 1993)

Lymphadenectomy	Total no. of patients	Average no. in a hospital	Hospital death (%)	Morbidity (%)	Hospital stay (days)
D1 gastrectomy	513	1.3	6.4	25.0	17.9
D2 gastrectomy	483	1.2	9.9	37.9	22.3
					From [16]

On average, one member hospital treated 1.3 patients in a year by D1 gastrectomy and 1.2 patients by D2 gastrectomy. Many specialists consider that this is not enough to master a new surgical procedure, and will be one of the causes of a high mortality rate [16, 17]. Reproduced by permission of Bonenkamp J, Songun I, van de Kerlde CJH *et al.* Randomized comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995, **345**, 745–748. © Lancet Ltd 1995.

INCREASE OF MORBIDITY AND MORTALITY AFTER LYMPHADENECTOMY

The operative mortality rate was very low in our series of gastric cancer patients treated over the 10-year period (1982–1991). We experienced only seven surgical deaths in 1895 patients treated by D2/D3 lymphadenectomy. The mortality rate was 0.4%, which was no different from that in the D0/D1 group; 0.5% (3/574). Our surgical complication rate was 21.9% in the D2/D3 group and 20.6% in the D0/D1 group. The Japanese Nationwide Registry reported that, between 1979 and 1982, 30-days postoperative mortality was 1.7% in 20 064 patients treated by gastric resection (Table 1) and 1.2% in D2 lymphadenectomy, 2.8% in D1, and 5.4% in D0 [12].

In the German trial of 1654 patients, the postoperative mortality rate was no different between the standard and radical resections; 5.2% and 5.0%, respectively [13]. Fayers and the British Stomach Cancer Group (32 centres) organised a multicentre trial to evaluate D2 dissection in 1986 [15]. This study used a teaching video to standardise the D2 operation, but most surgeons could not achieve the meticulous surgical technique required simply from a video. 37/400 patients died postoperatively (mortality rate 9.3%) (Table 1). The mortality in the D2 group was double that of the D1 patients (13% versus 6%).

Van de Velde understood the importance of standardisation of surgical techniques for the evaluation of D2 lymphadenectomy. When he organised a Dutch multicentre trial, he invited Sasako from the National Cancer Center, Tokyo, as the instructor. Even with his hard work during a 4 month stay in The Netherlands, it was very difficult to teach the details of surgical techniques to 80 member hospitals. In 1995, Bonenkamp and colleagues reported the early results of the Dutch trial, which showed that the D2 group had a significantly higher mortality rate (9.9%) than the D1 group (6.4%) [16] (Table 2).

Heated debate has appeared in the *Lancet* over the contrast between Japanese and Dutch trials [17]. Several factors have been considered, including the difference in patient characteristics and different perioperative management. Sue-Ling and associates pointed out that one member hospital treated only 1.2 patients by D2 gastrectomy in a year in the Dutch trial. He stressed that the number is not enough to master a new surgical procedure [18]. Siewert considered, from his experience in the German trial, that the Dutch results were due to inexperienced surgeons and unnecessary resection of the distal pancreas (unpublished personal communication).

We know that a randomised trial is essential for the evaluation of the benefits of lymphadenectomy. However, the D2 lymphadenectomy has been developed step-by-step over a period of 30 years, and Japanese people experienced and understood the effectiveness and safety in this long period. Under these circumstances, it is impossible to organise a controlled randomised trial in Japan. If we were to propose such a trial to our patients, they would immediately leave our hospital!

CONCLUSION

Japanese experience and some Western studies have shown a clear survival benefit for systematic LN dissection or D2 lymphadenectomy in the treatment of gastric cancer. We know that this surgical procedure is not simple. Surgeons must have a detailed knowledge of regional anatomy, pathology, and physiology. They should also be skilful in surgical techniques. Furthermore, careful postoperative care is important to minimise mortality and morbidity rates. We would like to propose that systematic LN dissection should be performed only by specialised surgeons in specialised centres. At present, this is the only way to minimise morbidity and mortality associated with surgery for gastric cancer, so that patients can benefit from the improved long-term survival which extended LN dissection can provide.

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DESPITE A decreasing incidence, carcinoma of the stomach is one of the main causes of cancer-related death worldwide. As chemotherapy has not proven very efficient, surgery is still the most important treatment of gastric carcinoma. Oncological surgery of most tumours includes the removal of the primary tumour and of the corresponding lymph nodes. As the surgeon cannot determine exactly during the operation which upper abdominal and perigastric lymph nodes are involved, the total removal of the regional lymph nodes is necessary [1]. This regimen is absolutely necessary in any radical tumour operation which aims at achieving local tumour absence (UICC-R_0) as a basis of healing. There is worldwide agreement concerning the extent of stomach resection. The removal of the corresponding lymph node stations is the object of many discussions.

The Japanese Research Society for Gastric Cancer has very accurately anatomically and clinically analysed the lymphatic drainage of the stomach. The results of these investigations have been published [2], and consequently in Japan an extended lymphadenectomy has been performed more often than in Western countries. This 'D2 lymphadenectomy' is at present not the standard treatment in other countries. Until recently, in the U.S.A. it was practised in less than 5% of operations [3]. The prognosis for carcinoma of the stomach is still poor, despite radical surgery. The overall 5-year survival rate in Western countries is approximately 20%, the 5-year survival rate for resected patients is approximately 30–35%, whereas in Japan it has been much higher for a long time (Table 1).

Different hypotheses have been suggested as an explanation: that the tumours differ in their biological behaviour; that the much higher incidence of early gastric cancer in Japan is the reason for the difference in survival rates; or because of a difference in treatment, especially the different extent of the lymphadenectomy. The hypothesis of different biological behaviour could be rejected by a comparative study [4]. A computer program designed in Japan for the pre-operative prognosis of lymph node metastases also rejected the hypothesis of biologically different diseases because of its easy and valid application on German patients [5].

The influence of differing staging systems in Japan and in Europe must also be dismissed as a cause for the differences. Patients with tumours of assimilated stage had better prognoses in Japan than in Western countries. The last remaining hypothesis concerns the difference in the treatments, which have differed over a long period of time as to the extent of the lymphadenectomy.

PRINCIPLES OF LYMPHADENECTOMY IN GASTRIC CARCINOMA SURGERY

According to the Japanese classification there are defined lymph node stations which are made up of several lymph node compartments. Which of the defined stations belong to which compartment varies slightly according to the location of the tumour. The first lymph node compartment normally contains the lymph nodes in the major and the minor stomach curvatures. The second compartment consists of lymph nodes in the region of the truncus coeliacus, of the common hepatic artery, of the left gastric artery, of the splenic artery and hilus. The third lymph node group contains stations in the liver hilus, in the transverse mesocolon and near to the pancreatic head, while the fourth group includes mainly