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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-R₀) 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

Table 1. Five-year survival rates (%) in Japan, Germany and the U.S.A.

[Ref.]	Years	No. of cases	Mortality (%)	5-year survival (%) / UICC stage					
				IA	IB	II	IIIA	IIIB	IV
Japan [22]	1979–1982	18 189	1.7	100	90	71	48	29	11
Germany [9]	1986–1989	803	5.0	86	69	55	38	17	16
U.S.A. [3]	1988	11 264	7.2	59	44	29	15	9	3

para-aortal lymph nodes. Accordingly, the removal of the various lymph node compartments is defined as follows: D1 lymphadenectomy is the removal of the perigastric nodes along the major and the minor stomach curvatures. D2 lymphadenectomy includes, apart from the removal of the first group, the removal of the lymph nodes of the second compartment, and so on. Based on previously mentioned anatomical and clinical studies, in Japan, the D2 lymphadenectomy has been the standard operation for at least two decades. Depending on the location and the size of the tumour, the lymphadenectomy can be further extended.

In Western countries, only the D1 lymphadenectomy has been performed over a long period of time. This difference in the procedures was thought to account for the differences in survival rate when comparing patients with tumours of the same stage from Japan and from Western countries. Consequently, in Western countries, studies were conducted on groups of patients who had undergone D2 lymphadenectomy.

WESTERN STUDIES ON LYMPHADENECTOMY

In order to evaluate the effect of D2 lymphadenectomy, numerous comparisons were made between groups of patients who had undergone D2 lymphadenectomy and former collectives of patients who had undergone D1 lymphadenectomy at the same institutions, showing that patients on whom D2 lymphadenectomy was performed had mostly prognostic advantages. Such comparisons cannot be accepted, because, apart from the extent of surgery, other factors of possible prognostic relevance could have changed compared with the historical control group. This is true for the steady improvement of the peri-operative management, for the pre-operative selection of patients, for the pathohistological

examination, and so on. Although the Japanese data, which were collected exclusively in retrospective studies, are impressive, randomised studies are required in order to prove the improvement of the prognosis by extending lymphadenectomy from the method of D1 to D2.

The first randomised study was carried out in South Africa. However, due to the design of the study, very few patients could be analysed. The results showed that the D2 lymphadenectomy group had no advantage in survival, but considerably more serious peri-operative complications [6]. The long-term analysis also revealed no difference between D1 and D2 patients regarding survival [7]. A randomised study from Hong Kong compared a D1 subtotal gastrectomy with a D3 total gastrectomy in patients with antrum carcinoma and revealed a better survival rate in patients from the D1 group [8].

The first prospective but not randomised study of a large number of patients was the German Gastric Carcinoma Study (GGCS) conducted by Siewert and colleagues [9] (Table 2). This study is important because it analysed almost 2000 patients. Only 0.8% of the patients were lost during the follow-up period. Approximately two-thirds of the patients had undergone a D2 lymphadenectomy. As to the extent of the lymph node dissection, there was the so-called 'standard dissection', in which less than 25 lymph nodes were removed, and the so-called 'radical dissection', in which more than 25 lymph nodes were removed. The number of lymph nodes to be removed was determined by the pathologist. For UICC tumour stages II and IIIA, significantly better 5-year survival rates were observed in the 'radical dissection' group than in the 'standard dissection' group. The 5-year survival rate for stage II was 55.2% (D2) and 26.8% (D1) and for stage IIIA 38.4% (D2) and 25.3% (D1).

Table 2. Studies comparing different types of lymphadenectomy

Author [Ref.]	Study	No. of cases	Years	5-year survival (months)		Significance
				D1	D2	
Dent [6]	rp	62	1982–1986	69	67	ns
Wanebo [10]	r	2124	1988	24.8	26.3	ns
Siewert [9]	p	1182	1986–1989			
UICC stage II				26.8*	55.2†	s
UICC stage IIIA				25.3*	38.4†	s
UICC stage IIIB				27.5*	17.5†	ns
MRC trial [11]	rp	400	1986–1993	?	?	?
Dutch trial [12]	rp	996	1989–1993	?	?	?
Median survival (months)						
				D1 subtotal gastrectomy	D3 total gastrectomy	
Robertson [8]	rp	54	1987–1991	50.4	30.7	s

* < 26 lymph nodes removed; † > 25 lymph nodes removed.

r, retrospective; p, prospective; rp, randomised and prospective; s, significant; ns, non-significant.

A retrospective analysis carried out in the U.S.A. on 3800 patients with curative resection could not reveal an improvement in the survival rate due to D2 lymphadenectomy in contrast to D1 lymphadenectomy [10].

Two European prospective randomised studies comparing D1 lymphadenectomy with D2 lymphadenectomy have not yet been completed and only interim reports are available. The British MRC trial and the Dutch DGCG trial are almost identical. Both trials compare randomised prospective patients with D1 lymphadenectomy with patients with D2 lymphadenectomy. So far, the results show a much higher mortality and morbidity for D2 patients [11,12], with mortality twice as high in the D2 compared with the D1 group. The higher rate of distal pancreatic resection and of splenectomy performed in order to guarantee the removal of the lymph nodes in this area, accounts for the increase in morbidity and mortality revealed in both trials. In the British trial, the rate of distal pancreatoco-splenectomies was 56%, and in the Dutch trial, 30% of the patients with D2 lymphadenectomy had also undergone distal pancreatic resection. The mortality was 10% in the Dutch trial and 13% in the British trial. So far, there are no data on 5-year survival, but the Dutch trial reported no difference in the 3-year survival between the two groups after curative resection [13]. Therefore, the Dutch trial group recommend: "Whilst we await survival results, D2 dissection should not be used as standard treatment for Western patients" [12].

DISCUSSION

The more extended lymphadenectomy on Japanese patients is, in comparison with historical groups of patients, the only possible explanation for the higher survival rate. Recurrences after curative resection are mostly located extra-luminary, distant metastases as the first symptom of an advanced disease being rare. In 44% of 107 patients who had undergone second-look surgery, locoregional recurrences with no distant metastases were found [14]. Therefore, the aim to lower recurrences by applying a more extended lymphadenectomy is logical. The studies conducted on Western patient groups were, unfortunately, poorly designed. The first randomised comparisons [6,8] could not provide reliable substantial results because, according to the study protocol, very few patients could be analysed or because the study groups did not differ only in the extent of the lymphadenectomy. The very extensive German study [9] has the disadvantage of not being randomised. Furthermore, some of the participating institutions as a matter of principle executed only D1 lymphadenectomy. The definition of the groups 'radical dissection' versus 'standard dissection' is made exclusively according to the number of detected lymph nodes and is not based on the exact anatomical terms of the Japanese system. However, it can be assumed that removing 25 lymph nodes can only be achieved by performing a dissection based on the Japanese principle of D2 lymphadenectomy. This is expected, due to a systematic analysis of the number of upper abdominal lymph nodes in corpses [15]. However, there still remains a source of possible errors. The British and the Dutch prospective randomised trials neither have the disadvantage of the American study of Wanebo and colleagues of being retrospective, nor the disadvantage of a large number of involved institutions with no steady therapeutical method. However, the relevance of these studies is endangered because an unusually high percentage of patients of the

D2 group had undergone resections of the pancreas or splenectomy. Normally, resection of the pancreas and of the spleen is not a *conditio sine qua non* for radical lymphadenectomy in this region. Using a pancreas-preserving surgical method, complications and mortality due to resection can be avoided [16]. Thus, as soon as the 5-year results of the Dutch and British trials are available, part of the surgical method might already be obsolete, due to the natural progress of the surgical technique for gastric carcinoma. However, it will be interesting to see how frequently involved lymph nodes will be detected by this surgical method in the regions of the spleen artery and the spleen hilus.

A further problem in the evaluation of results concerning the differences between D1 and D2 lymphadenectomy is the phenomenon of stage migration. It is particularly important when comparing a group from the present with historical controls. It is also known by the name of "Will Rogers" phenomenon and was described for the first time for bronchial carcinoma [17]. The removal of a greater number of lymph nodes will result in a greater number of involved lymph nodes. Consequently, some patients who, for instance, would correspond to stage II in the case of a D1 lymphadenectomy, would be allocated to stage IIIA following a D2 lymphadenectomy. This would result in patients having a relatively poor prognosis changing stage migration after a D2 lymphadenectomy from a lower stage to a higher stage, resulting in a relatively good prognosis among the patients of this stage. The lower stages are quasi cleared of patients with a comparatively poor prognosis. Apart from the changed surgical technique, a more sensitive pathological technique can also have this effect. This phenomenon alone can lead to differences in the 5-year survival rates of individual groups of patients. However, this will not influence the overall survival rate.

An intra-individual comparison of D1 lymphadenectomy with D2 lymphadenectomy in patients whose specimen of D1 and D2 lymphadenectomy were resected and analysed separately made clear that due to the 'Will Rogers' phenomenon approximately 20% were moved from stage II to stage IIIA and more than 60% from stage IIIA to stage IIIB. This could be observed in 17.9% of the patients of the entire study group. The only group with a statistically significant improvement in prognosis between D1 and D2 lymphadenectomy were stages II and IIIA [18].

In the prospective non-randomised German Gastric Carcinoma Study, stage migration could be observed in 12.1% of patients. Thus, the advantage in the prognosis for stages II and IIIA after curative D2 lymphadenectomy could only be slightly influenced [19]. German studies have shown that patients with pN0 and pN1 carcinoma of the stomach benefit from D2 lymphadenectomy [20,21]. However, lymphadenectomy in pN0 tumours by definition cannot increase the radicality. These facts are contradictory. This explanation was found by the immunohistological analysis of lymph nodes, which revealed a so-called microinvolvement. Thus, it is possible to achieve a prognosis-relevant increase of radicality by removing lymph nodes with microinvolvement but with no evidence of typical metastases [20].

The available studies reflect the high degree of uncertainty concerning the relevance of D2 lymphadenectomy for the prognosis of gastric carcinoma. Clear evidence for the prognostic relevance of D2 lymphadenectomy is lacking. Thus, the rationale concerning D2 lymphadenectomy exists only on the basis of theoretical and clinical findings of the Japanese

surgeons. Studies have revealed that patients with carcinoma of the stomach who were also submitted to a treatment similar to the Japanese technique, have so far shown no improvement in prognosis to the extent which one would expect according to the Japanese data.

Thus, there are many objections to the existing data concerning the prognostic relevance of D2 lymphadenectomy. Reliable and reproducible evidence for the improvement of the prognosis for gastric carcinoma by means of D2 lymphadenectomy is still lacking. Based on these facts, the recommendation of D2 lymphadenectomy as a regular component of gastric cancer therapy cannot be considered proven and is, therefore, not justified. However, there also exist prospectively collected data showing that D2 lymphadenectomy *per se* does not entail a danger for the patients. Therefore, it seems appropriate to recommend, as a treatment for gastric carcinoma, the D2 lymphadenectomy, without necessarily performing a resection of the pancreas. Only by this strategy can we ensure that our patients benefit from the D2 lymphadenectomy which, so far, because of academic discipline, cannot be considered as proven.

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