

# Gastric cancer: staging and surgery

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## Introduction

Because of its poor prognosis and for being the most frequent cause of cancer-related death worldwide, gastric cancer used to be called the 'captain of death'. Even though its mortality rate has gradually decreased, this decrease is mostly attributable to its worldwide declining incidence. However, gastric cancer is still the second most common cause of cancer-related death in the world [1]. Surgery remains the cornerstone of treatment for gastric cancer, but little of the surgical approach has remained the same since Japanese investigators started reporting better survival rates for all stages. These investigators have ascribed their superior survival rates to early detection and extensive lymphadenectomy [2, 3]. In Japan, so-called early gastric cancer (tumour confined to mucosal or submucosal layers) is found in up to 40% of patients and an extended lymph node dissection (D2) is employed as standard surgical procedure, while in Western countries a limited lymphadenectomy (D1) is generally employed. The Japanese have argued that D2 resection should be performed in all patients with invasive gastric carcinoma, including those with early gastric cancer and that a D3 lymphadenectomy should be performed in all patients with advanced gastric cancer with serosal invasion [4, 5]. However, the Japanese results are based on retrospectively collected data only. Therefore, improved results of surgical treatment of gastric cancer in Japan may not only be attributable to extensive lymph node dissection, but also to the fact that early gastric cancer and other more favorable prognostic factors are much more common. Besides, in most Western countries lymph nodes are regarded as indicators rather than governors of disease [6]. According to this theory, extended lymph node dissection merely improves the accuracy of tumour staging and thus induces a so-called stage migration by which a better stage-specific survival will be achieved, while the overall survival is not altered. If we want to develop and apply new diagnostic and therapeutic approaches for a disease this common, with such a poor prognosis, we have to treat our patients in (good quality) controlled randomized multicenter clinical trials before introducing new approaches in daily practice.

## Staging

To end the confusion caused by different definitions of the R-classification in the Japanese and the International Union

Against Cancer (UICC) nomenclatures, in September 1993 it was recommended (at a meeting of the World Health Organization Collaborative Cancer Group) that the 'D'-classification be used to indicate the extent of lymph node dissection and the 'R'-classification be used to indicate the residual tumour-situation after resection [7]. According to the rules of the Japanese Research Society for Gastric Cancer (JRS GC), the stomach is divided into three sectors: upper third (or C); middle third (or M) and lower third (or A). The exact nodal groups that require removal for potentially curative resection depend on the location of the primary tumour. A D1 resection removes all N1-level (along the splenic and left gastric artery and coeliac axis) nodes and a D3 resection removes N1, N2 and N3-level (hepatoduodenal and root of the mesentery) nodes [8]. In the R-classification, R0 means no residual tumour (macroscopical and microscopical no residual tumour), whereas R1 means microscopical residual tumour and R2 means macroscopical residual tumour.

In order to find an explanation for the discrepancy in survival rates between Japan and Western countries, patient data from Japan, Germany and the Netherlands were compared. This study showed that imbalances in prognostic factors and staging systems could not explain satisfactorily the differences in 5-year survival rates, suggesting that the better outcome in Japanese patients could be treatment-related [9].

## Randomized trials on extent of lymphadenectomy

To analyze the role of extended lymphadenectomy and extent of gastrectomy (total versus subtotal) for gastric cancer treatment, several prospectively randomized trials were undertaken in Western countries. The first randomized trial dealing with the issue concerning the place of extended lymph node dissection (D2) in the treatment of gastric cancer by Dent et al. (South Africa) [10] warned against extended lymph node dissection. D2 resection was associated with a greater blood transfusion requirement, increased morbidity and a longer hospital stay, while there was no survival advantage. The fact that 403 patients were randomized in this trial and that only 43 patients (11%) were eligible made the interpretation of these results very difficult. More than 6 years later, a second warning came from Hong Kong [11]. In this trial, comparing D1 subtotal gastrectomy with D3 total gastrectomy in patients

with antral carcinoma, increased morbidity (intra-abdominal sepsis) associated with extended dissection was again demonstrated. Although the patients in the D1 group had a significantly better survival than the patients in the D3 group, a straight forward interpretation of this finding was not possible. This is because the number of the analyzed patients was small; also subtotal gastrectomy combined with limited lymphadenectomy (D1) was compared with total gastrectomy combined with extended lymphadenectomy (D3), while the extent of lymphadenectomy, as well as the place of total and subtotal gastrectomy, are still debated in gastric cancer surgery. In a prospective controlled study comparing total and subtotal gastrectomy for antral carcinoma by Gouzi et al. (France) [12] no difference in postoperative mortality and survival rate was found. However, in another study by Bozzetti et al. (Italy) [13], in interim analyses increased morbidity and mortality was found in patients undergoing total gastrectomy, while survival results are still awaited.

Two other prospectively randomized trials, one in the Netherlands by the Dutch Gastric Cancer Group (DGCG) and the other in the UK by the Medical Research Council (MRC), comparing D1 with D2 dissection were completed in 1993. In the DGCG trial 1078 patients were entered, 711 of whom underwent a curative resection in intent. In the UK MRC trial 400 patients were included. Strict quality control measures were taken in the DGCG trial to guarantee the intended difference between these two resection types [14]. ‘Contamination’ (dissection of lymph nodes outside the indicated area) and ‘non-compliance’ (incomplete lymph node dissection) were defined and acknowledged as possible confounders of outcome. Also, the beneficial effect of extended lymph node dissection by stage migration was assessed in this trial [15]. Both these trials, which included a large number of patients, demonstrated that extended lymphadenectomy is associated with significantly higher morbidity and mortality rates compared with limited lymphadenectomy [14, 16].

Despite numerous retrospective comparisons of limited and extended lymphadenectomy in which a survival advantage was found in patients undergoing extended lymphadenectomy for gastric cancer (of which the German multicentre observation study [17] is the most important one) a beneficial effect on survival remains to be demonstrated in prospectively randomized trials. Although these types of studies are very important, their applicability in general practice is not possible, because of a case selection bias due to the nature of every retrospective analysis. In a meta-analysis of randomized trials studying the effect of adjuvant chemotherapy after a curative resection, only a marginal survival advantage was found [18].

### How can we decrease morbidity/mortality of extended lymphadenectomy?

Randomized trials with a large number of patients demonstrated that extended lymphadenectomy (D2 and D3) is asso-

ciated with significantly higher morbidity and mortality compared with D1 resection. Even though a selection bias (inclusion criteria) is inevitable in trials, these multicenter trials do give a good reflection of the present situation, because they are the closest to the real situation. Five-year survival rates were similar in the two groups: 45% for the D1 group and 47% for the D2 group [95% confidence interval (CI) for the difference, -9.6% to +5.6%]. The patients who had R0 resection (i.e. who had no microscopical evidence of remaining disease), excluding those who died postoperatively, had cumulative risks of relapse at 5 years of 43% with D1 dissection and 37% with D2 dissection (95% CI for the difference, -2.4% to +14.4%). Patients with lymph node metastases limited to the first echelon (N1), generally with stage II and IIIA disease, may benefit from D2 dissection. Another aspect which is still not clear is who should perform these operations [19]? However, it is probable that gastric cancer is treated best by a multidisciplinary team with a committed surgeon, pathologist, radiologist and medical-oncologist. In addition, perioperative care deserves more attention, as morbidity rates from extended lymphadenectomy in Japan, where gastric cancer surgery is performed by gastric cancer surgeons only, are as high as in the West, but without the increased mortality. These facts can not be fully explained by patient- or tumour-related factors, such as age, weight, height/weight index and concomitant disease [9, 20]. In order to minimize the complications associated with pancreatic tail resection and splenectomy, the Japanese have developed pancreas- and spleen-preserving techniques. The results achieved with these methods justify a more refined surgical approach: pancreatectomy and splenectomy ‘de necessitate’ should be applied instead of ‘de principe’ [21, 22].

### Multimodality treatment

Preoperative (neoadjuvant) systemic chemotherapy seems a promising approach. By giving systemic treatment, both the primary tumour as well as distant (micro) metastases can be handled, which may lead to downstaging. Therefore, it is expected that more patients can have resections, either for cure or for palliation, leading to an improvement of the survival rates and quality of life. The value of preoperative FAMTX (5-fluorouracil, doxorubicin and methotrexate) in operable gastric cancer was investigated in the Netherlands in a prospective randomized trial of which the end results will be presented. Currently a joint study with ECF (epirubicin, cisplatin and 5-fluorouracil) by the MRC is ongoing.

Trials are the only way of developing future standardized treatments without exposing our patients to unproven and thus potentially dangerous treatment fads.

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#### Appendix 1. Gastric cancer staging

Classification	Definition
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma <i>in situ</i> ; intraepithelial tumor without invasion of lamina propria
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades the muscularis propria of the subserosa
T3	Tumor penetrates the serosa (visceral peritoneum) without invasion of adjacent structures
T4	Tumor invades adjacent structures
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–6 regional nodes
N2	Metastasis in 7–15 regional nodes
N3	Metastasis in >15 regional lymph nodes
Distant metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

**Appendix 1.** *(continued)*

AJCC/UICC stage grouping	Primary tumor (T)	Regional lymph nodes (N)	Distant metastasis (M)
Stage 0	Tis	N0	M0
Stage 1A	T1	N0	M0
Stage 1B	T1	N1	M0
	T2a/b	N0	M0
Stage II	T1	N2	M0
	T2a/b	N1	M0
	T3	N0	M0
Stage IIIA	T2a/b	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T3	N2	M0
Stage IV	T4	N1–3	M0
	T1–3	N3	M0
	Any T	Any N	M1

AJCC, American Joint Committee on Cancer; UICC, Union Internationale Contre le Cancer.