

# Historical assumptions of lymphadenectomy

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**Abstract:** The role of lymphadenectomy for the treatment of gastric cancer is still very much open to debate. Consequently, Japanese, European and American surgeons perform different typologies of lymphadenectomy because of the absence of randomized clinical trials confirming the superiority of extended lymphadenectomy over less invasive surgery. In Japan, D2 lymphadenectomy has been considered as the gold standard for advanced gastric carcinoma for many years. Although numerous European studies have been conducted in an attempt to find differences between D1 and D2 lymphadenectomy, none has succeeded to date. The decision to wait for results attesting to the fact that D2 guarantees a better outcome than D1 resulted in a long delay in the implementation of D2 as the gold standard treatment in Europe. In the U.S., the study by Macdonald *et al.* established D1 lymphadenectomy followed by chemoradiotherapy as the treatment of choice for advanced cancer, whereas D2 is officially indicated as the gold standard in the most recent European guidelines [the Italian Research Group for Gastric Cancer (GIRGC), German, British, ESSO]. Interestingly, European guidelines for lymphadenectomy are not based on evidence-based medicine but rather on the experience of the most important centers involved in the treatment of gastric cancer.

**Keywords:** Gastric cancer; D1 lymphadenectomy; D2 lymphadenectomy; Maruyama index; super-extended lymphadenectomy

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## Introduction

The role of lymphadenectomy for the treatment of gastric cancer has long been considered a never-ending story. In fact, studies and trials performed over the past 40 years have not added any substantial information to what was already known and consequently there are still no evidence-based recommendations for the procedure in this setting. Although lymphatic diffusion is considered to be an independent significant prognostic factor, extended lymphadenectomy (D2) is frequently recommended in the East, has been implemented in several European countries in recent years, and is optional in the U.S.

In Japan, notwithstanding the absence of randomized

clinical trials, D2 lymphadenectomy has been considered the gold standard for patients with locally advanced gastric carcinoma since the 1980s. The overall survival (OS) of these patients is substantially higher than that of their western counterparts (1-3). The resistance shown by European and North American surgeons to follow in the footsteps of their Japanese colleagues stems from their reluctance to subject patients to surgical procedures that are much more invasive than D1 lymphadenectomy, have a higher incidence of surgical complications and postoperative mortality, and are not backed up by evidence from clinical trials attesting to the superiority of D2 over D1 lymphadenectomy in terms of OS and disease-free survival (4,5).

In 1993 Siewert *et al.* published the results from the first important prospective, multicenter clinical trial on lymphadenectomy (not yet classified as D1 or D2) carried out in the West by the German Gastric Carcinoma Study Group. The authors reported an improved outcome for patients who were submitted to lymphadenectomy with the removal of more than 25 lymph nodes (6). However, the decision of Western surgeons to wait for significant results from clinical trials before changing their surgical behaviour, coupled with the refusal of eastern colleagues to perform D1 lymphadenectomy because they considered it inadequate, led to a delay of several years in the implementation of a clinical practice that is now recommended in almost all European National Guidelines (7-11). Interestingly, the European guidelines are not based on evidence-based medicine because no definitive trials have been conducted in this setting to date (12).

### The Japanese progress

In 1989 Maruyama published a clinical study in which 1,931 patients with gastric cancer were classified according to seven parameters (age, sex, Borrmann morphological classification, degree of tumor infiltration, site of tumor, maximum tumor diameter and histological type). The study considered nodal involvement in patients with similar neoplasms (reported as a percentage). During follow-up, the rate and site of recurrence were recorded (The Maruyama program), permitting a comparison between patients and facilitating the decision about which type of lymphadenectomy to perform (13). In 2002, Japanese Guidelines (published in English), which took into account the long-standing experience of Japanese surgeons in the field, identified D1 lymphadenectomy as “adequate” for early gastric cancer and recommended D2 lymphadenectomy for locally advanced disease (14).

### The Western clinical trials

The Maruyama program was validated by numerous western studies (15,16), but the need for significant results led to two randomized clinical trials being conducted: the Dutch trial (17) and the British trial (18). Although neither reported significant differences between D1 and D2 patients, the D2 group showed higher perioperative morbidity and mortality.

In the Dutch trial (published in 1999) (17), 711 patients with gastric carcinoma were randomized to undergo

gastrectomy and D1 or D2 lymphadenectomy. OS was 45% and 47% for D1 and D2 patients, respectively. A significant difference in postoperative mortality was seen between the two groups; 25% for D1 and 43% for D2. Thirty-day postoperative mortality, albeit not significant, was higher in D2 patients. The British trial, also published in 1999, showed similar results to the Dutch trial. In particular, morbidity and mortality worsened after spleno-pancreatectomy, a procedure considered necessary by surgeons in the East to obtain a more complete lymphadenectomy. In the U.S., extended lymphadenectomy is still only performed in a few centers and D1 lymphadenectomy remains the standard treatment for locally advanced gastric cancer. In 2001 Macdonald *et al.* published a randomized clinical trial in which patients submitted to gastrectomy and D1 lymphadenectomy were compared with those who underwent the same treatment plus chemoradiotherapy. The latter group showed a significantly better outcome, suggesting the superiority of chemoradiotherapy over D1 dissection alone (19). Although the adjuvant treatment caused the severest toxicity (17% of patients did not finish the planned chemoradiotherapy), a better 5-year OS was observed in the D1 lymphadenectomy and chemoradiotherapy group (median OS in the surgery only group was 27 months compared to 36 months in the chemoradiotherapy group), together with a better control of local recurrence.

### The clinical trial by Wu *et al.* and the Italian Research Group for Gastric Cancer (GIRGC) studies

The study carried out in 2004 by Wu *et al.* on the complications of D1 and D2 lymphadenectomy showed a higher incidence of complications in D2 patients but no significant difference in mortality between the two groups (20). A follow-on study published in 2006 by the same authors revealed a better outcome for D2 patients (21). Results from a clinical trial conducted in the early 2000s by GIRGC showed a higher incidence of complications in D2 than in D1 procedures without, however, a significant difference in mortality (22). de Manzoni *et al.* (23) observed that the number of lymph nodes removed increased as the extent of lymphadenectomy increased, leading to a change in tumor staging (TNM). However, it was also seen that that there was no change in the TNM stage when more than 30 lymph nodes were removed (23).

## The Maruyama index

Two authors of the Dutch trial, Peeters in 2005 (24) and Hundahl in 2007 (25), proposed the Maruyama index as a prognostic factor. Based on Maruyama's case series in which a risk of positivity (reported as a percentage) was assigned to each lymph node station (13), these authors established the "Maruyama index of unresected disease (MI)", a simple sum of the risk percentages of lymphatic stations not removed by surgery. The index proved to be correlated with survival, patients with MI <5 showing a better 5-year survival than those with MI  $\geq$ 5 (13).

Hundahl's study, analysing survival curves and disease-specific survival rates, showed that MI <5 was an independent predictive factor of survival (25). The authors also reported data on 441 patients of the Dutch trial who subsequently died and were submitted to autopsy: 25 patients with MI <5 were found to have a lower incidence of local recurrence than those with MI  $\geq$ 5 (8% *vs.* 21%, respectively) (25).

## Recent studies

Fifteen-year follow-up data of the Dutch trial were published in 2009. Excluding patients who died of surgical complications from spleno-pancreatectomy, a procedure no longer included in gastric cancer treatment guidelines, a trend emerged towards an inversion of previous survival data, with overall survival rates of 29% and 21% for D2 and D1 lymphadenectomy, respectively (26).

In 2014 Degiuli *et al.* published the results from a randomized clinical trial in which 267 patients submitted to D1 or D2 lymphadenectomy did not show a significant difference in survival (27). However, a closer look at the study reveals that numerous patients considered as D1 actually underwent a more extended lymphadenectomy, resulting in substantial uniformity between the two procedures.

## The super-extended lymphadenectomy

Whilst D2 lymphadenectomy is an established practice in experienced surgical centers, the super-extended lymphadenectomy (D3) remains a controversial issue. The removal of para-aortic lymph node stations [para-aortic node dissection (PAND)] for locally advanced gastric cancer was advocated by Japanese surgeons in the past. However, the clinical trial by Sasako *et al.* in 2008 (28) comparing patients submitted to D2 lymphadenectomy with or without

removal of the para-aortic nodes did not reveal a significant difference in overall or recurrence-free survival (69.2% for D2 alone *vs.* 70.3% for D2 plus PAND). Following these results, Japanese surgeons abandoned prophylactic PAND and the procedure is no longer included in the Japanese Gastric Cancer Association (JGCA) guidelines (29). A comment is warranted on Sasako's study: first, patients with para-aortic metastases detected during preoperative staging were excluded, resulting in a very low incidence of involved lymph nodes (8.5% of patients with a 5-year survival rate of 18.2%). Patients diagnosed with positive para-aortic lymph nodes underwent adjuvant therapy only upon relapse. Of note, N0 patients submitted to PAND showed a better 5-year survival than those not submitted to this procedure (96.8% D2 lymphadenectomy plus PAND *vs.* 78.4% D2 lymphadenectomy alone).

Union for International Cancer Control (UICC) TNM staging of gastric tumor considers para-aortic lymph node lesions (M1) as metastatic disease (30). Conversely, several studies, including some conducted by Western authors have reported that patients with para-aortic lymph node involvement show a survival rate of around 17%, higher than that for other distant metastases. The advent of neoadjuvant chemotherapy for tumors with para-aortic involvement and the use of more effective chemotherapy to control advanced disease has recently led to a positive re-evaluation of the usefulness of the PAND procedure (31-33).

## Conclusions

Although D2 lymphadenectomy is now a much more frequent practice in the West, there is still great controversy about the D3 procedure. As pointed out by Verlatto *et al.* (12), although western trials strongly influenced evidence-based medicine, findings on lymphadenectomy were ultimately not taken into consideration by the authors of European guidelines (Italian, English, German) who acknowledge D2 lymphadenectomy as the gold standard for the treatment of advanced gastric tumor (as proposed by Japanese authors in the 1980s).

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest

to declare.

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