



# Do all the European surgeons perform the same D2? The need of D2 audit in Europe

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## Abstract

Although D2 lymphadenectomy is the standard of care for radical intent surgical treatment of gastric cancer, the real compliance with D2 dissection in Europe is still unknown. The aim of the present study is to analyze the variation in lymph-node harvesting reported after D2 dissection in European series and to present a European project aiming at evaluating the real compliance with D2 lymphadenectomy. A PubMed search for papers using the key words “D2 lymphadenectomy” and “gastric cancer” from 2008 to 2017 was undertaken. Only studies by European authors in English language reporting the number of retrieved lymph nodes after D2 lymphadenectomy were included. The results of literature review were descriptively reported. The literature survey yielded 16 studies: 2 RCTs, 3 observational multicentre studies, and 11 observational monocentric studies. A large variability was found in the number of retrieved nodes, which, overall, was the lowest in the surgical series from Eastern Europe (16.6 and 19.9 in the Lithuanian and Hungarian series, respectively) and the highest in an Italian RCT. The within-study variability was also quite high, especially in multicentre RCTs and observational studies. Sample size tended to have a larger effect on the variability of lymph nodes retrieved than on its actual value. However, in both cases, the relation was not significant, due to the low number of studies considered. There is a large variability in the number of retrieved nodes after D2 dissection in European series. This reflects, at least partly, different approaches to D2 lymphadenectomy by European surgeons and may be responsible of the different outcomes observed in patients with gastric cancer across Europe. Therefore, there is the need to standardize the practice of D2 gastrectomy in Europe and to define possible variations of D2 procedures according to tumour’s characteristics.

**Keywords** D2 lymphadenectomy · Standardization · Retrieved lymph nodes

## Introduction

According to many European guidelines, D2 lymphadenectomy is the standard of care for radical intent surgical treatment of gastric cancer [1–4]. However, the real compliance with D2 dissection in Europe is still unknown. The Dutch

Gastric Cancer Group pointed out that, in their trial [5], 84% of patients in the D2 gastrectomy group had less dissection than specified in the protocol. Major non-compliance, defined as the absence of retrieved lymph nodes in more than two nodal stations included in the intended extent of D2 dissection, occurred in 26% of cases. The limited adherence to the planned lymphadenectomy in the Dutch trial very likely reflected the learning curve for extended lymphadenectomy. Similarly, Markar et al. [6] extensively assessed the quality of surgery within randomised-controlled trials of the treatment of gastro-oesophageal cancer from both Eastern and European countries and reported a high variability of lymph-node harvest after gastrectomy in surgery-alone arms. In more recent European trials where the learning curve effect is likely to be more limited, the number of centres and the patient-to-centre ratio were associated with a rise in variability of lymph-node harvest [6].

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It is very possible that the issue of compliance to the D2 procedure does not only affect the RCTs. A recent overview [7] focused on the outcomes of gastric cancer surgery in Europe showed a significant relationship between hospital volume and operative mortality, but also suggested that differences in outcomes between several European countries could not be explained by differences in hospital volumes alone. Variations in the approach to D2 lymphadenectomy may also contribute to discrepancies in gastric cancer survival observed across European countries.

The aim of the present study was to analyze the variation in lymph-node harvesting reported after D2 dissection in European series and to present a European project aiming at evaluating the real compliance with D2 lymphadenectomy.

## Methods

A PubMed search for papers using the key words “D2 lymphadenectomy” and “gastric cancer” from 2008 to 2017 was undertaken (MB). Only studies by European authors in the English language reporting the number of retrieved lymph nodes after D2 lymphadenectomy were included. Series of patients treated with neo-adjuvant chemo or chemo-radiotherapy were excluded as the preoperative treatment could have affected lymph-node harvesting. Similarly, considering that mini-invasive gastrectomy is not a standard procedure in Europe, due to the possible effects of learning curve on post-operative outcomes, papers reporting outcomes of laparoscopic or robotic resection for gastric cancer were not included. In addition, papers whose inclusion criteria

were restricted to specific tumour stages risking a significant selection bias were excluded.

The results of literature review were descriptively reported. For papers showing the mean number of retrieved nodes, the coefficient of variation (CCV), to measure the degree of variation between different series, was calculated as the ratio of the standard deviation to the mean. The association between sample size and mean or CV of retrieved nodes was evaluated by Spearman’s rank correlation coefficient.

## Results

The literature survey yielded 16 studies [8–23]: 2 RCTs [8, 9], 3 observational multicentre studies [10–12], and 11 observational monocentric studies [13–23] (Table 1). The number of retrieved nodes after D2 dissection is summarized in Table 2. A great variability among the studies emerged in the descriptive statistics employed. The median and range were the most appropriate statistics, given the asymmetric distribution of the variable under study, and were correctly used by seven studies [8, 9, 11–13, 16, 20, 21].

A large variability was found in the number of retrieved nodes, which overall was the lowest in the surgical series from Eastern Europe (16.6 and 19.9 in the Lithuanian [19] and Hungarian [20] series, respectively) and the highest in an Italian RCT [9]; [the range was narrower in the median number of retrieved nodes, varying from 24 [11] to 37 [13, 16] (Table 2)].

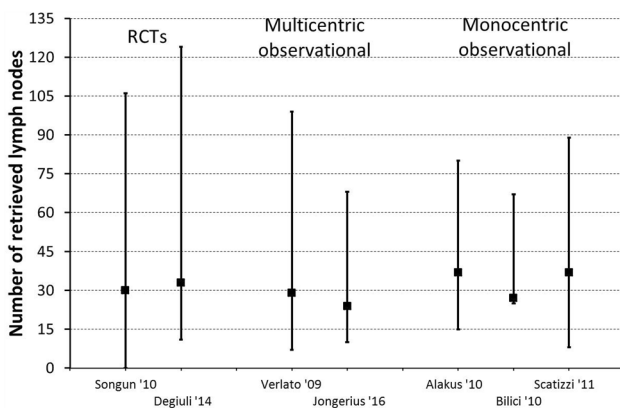
**Table 1** European studies on gastric cancer surgery, reporting number of retrieved nodes after D2 lymphadenectomy, published between 2008 and 2017 on journals indexed on PubMed

First author	Country	Year	Type of study	Mono/multicentre study	Type of lymphadenectomy
Songun [8]	NL	2010	RCT	Multicentre	D2
Degiuli [9]	Italy	2014	RCT	Multicentre	D2
Kung [10]	Sweden	2017	Observational	Nation-wide	D1+/D2
Jongerius [11]	NL	2016	Observational	Multicentre	Modified D2
Verlato [12]	Italy	2009	Observational	Multicentre	D2
Alakus [13]	Germany	2010	Observational	Single centre	D2
Muratore [14]	Italy	2009	Observational	Single centre	D2
Caruso [15]	Italy	2011	Observational	Single centre	D2
Scatizzi [16]	Italy	2011	Case/control	Single centre	D2
Luna [17]	Spain	2013	Observational	Single centre	D2
Diaz de Liano [18]	Spain	2008	Observational	Single centre	D2
Kavalakuskas [19]	Lithuania	2016	Observational	Single centre	D2
Toth [20]	Hungary	2013	Observational	Single centre	Modified D2
Bilici [21]	Turkey	2010	Observational	Single centre	D2
Sakcak [22]	Turkey	2011	Observational	Single centre	D2
Vural [23]	Turkey	2013	Observational	Single centre	D2

**Table 2** Number of retrieved lymph nodes in European studies reporting surgical outcomes of D2 lymphadenectomy, published between 2008 and 2017 on journals indexed on PubMed

First author	Year	Sample size	Retrieved nodes median (range)	Retrieved nodes mean (sd, CV%)
Songun [8]	2010	331	30 (0–106)	31.5
Degiuli [9]	2014	134	33 (11–124)	37
Kung [10]	2017	204 (TG)	–	29 (17, 58.6%)
Kung [10]	2017	54 (STG)	–	24 (14, 58.3%)
Jongerius [11]	2016	100	24 (10–68)	–
Verlato [12]	2009	584	29 (7–99; IQR 21–38)	30.9 (13.2, 42.7%)
Alakus [13]	2010	159	37 (15–80)	–
Muratore [14]	2009	200	–	25.9
Caruso [15]	2011	120	–	31.7 (15.6, 49.2%)
Scatizzi [16]	2011	30	37 (8–89)	–
Luna [17]	2013	44	–	36.6
Diaz de Liano [18]	2008	126	–	32.5 (IQR 16)
Kavalakuskas [19]	2016	228 (STG)	–	16.5 (6.8, 41.1%)
Toth [20]	2013	40	Range 10–38	19.9
Bilici [21]	2010	111	27 (25–67)	–
Sakcak [22]	2011	120	–	23.5 (9.3, 39.6%)
Vural [23]	2013	48	–	31.8 (16.1, 50.6%)

*IQR* interquartile range, *TG* total gastrectomy, *STG* subtotal gastrectomy



**Fig. 1** European studies reporting the number of retrieved nodes after D2 as median and range

When the number of retrieved nodes was reported for the subsequent period within the same study, a moderate learning curve was apparent. Indeed, in a Spanish study [17], the average number of retrieved nodes increased from 28.8 in the first 13 patients to 39.8 in the subsequent 31 patients. The increase in retrieved nodes was less apparent in a larger GIRCG study [12], where the median (range) increased from 28 (7–88) in the first half of the series ( $n = 276$ ) to 31 (8–99) in the second half ( $n = 308$ ).

The within-study variability was also quite high, especially in multicentre RCTs and observational studies (Fig. 1).

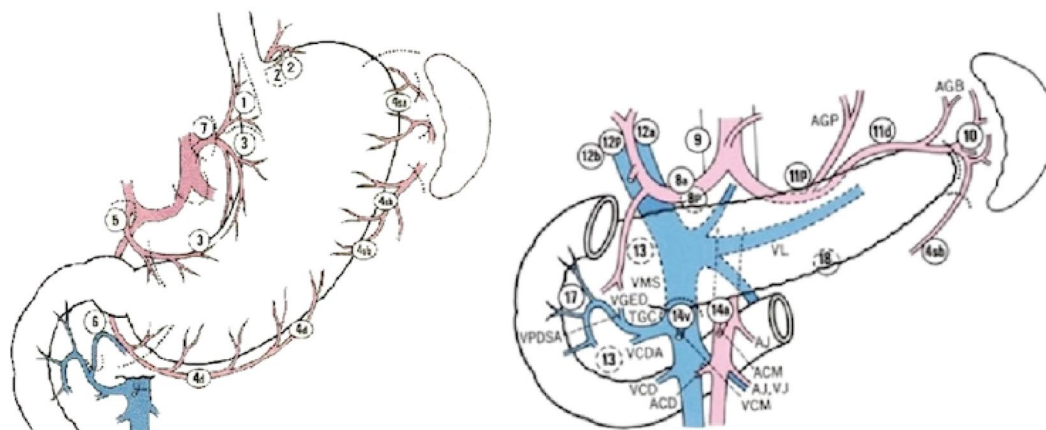
Sample size tended to have a larger effect on the variability of lymph nodes retrieved than on its actual value. Indeed, when considering only single centre studies, the association between sample size and CV of retrieved nodes tended to be stronger (Spearman’s rho = -0.63;  $n = 4$ ;  $p = 0.37$ ) than the association between sample size and average number of retrieved nodes (Spearman’s rho = -0.40;  $n = 7$ ;  $p = 0.38$ ). However, in both cases, the relation was not significant, due to the low number of studies considered.

## Discussion

Although the optimal extent of lymphadenectomy for gastric cancer has been debated in Europe for long time, there is currently general agreement that D2 dissection should be the standard of care for procedures with curative intent [24]. However, some variation seems to persist in the approach to D2 lymphadenectomy among European surgeons, and this variation could partly contribute to survival differences observed after radical gastrectomy for cancer across Europe. To date, no detailed systematic data on the compliance to D2 dissection in Europe are available.

The present review took into account the European studies reporting surgical outcomes after D2 lymphadenectomy, and found that, in all series, the average and/or median values of harvested lymph nodes were higher than 15, which is the cutoff recommended by the American Joint Committee on Cancer (AJCC) [25] as a minimum standard to ensure a proper tumour staging. These findings are consistent with

Please mark for each case which nodal station you would remove (the position of the tumour is marked in each diagram with the red dot):



**Fig. 2** D2 Audit web questionnaire: for clinical scenarios described in Table 3 (questions 1–14), each surgeon should mark the lymph nodes that he would remove using the following diagram

the previous reports, showing that intended D2 dissection is associated with a higher number of adequate lymphadenectomies, i.e., more than 15 excised nodes, compared to more limited dissections [12]. However, other useful statistics, such as the 25th percentile, were never reported except in one study [12], so that it was not possible to properly evaluate adequacy of tumour staging across Europe.

A large variability in the number of retrieved nodes was observed between different studies as well as within each single study, when considering either the range or the coefficient of variation. These results are similar to those already reported from the in-depth analysis of quality of surgery within the RCTs for the treatment of gastro-oesophageal cancer [6]. The observed variability may be due to different surgical technique, differences in pathologist experience, and extent of nodal examination or to differences in the natural number of lymph nodes for each patient.

Since the observed variability partly reflects differences in a surgeon's performance, there is a need to standardize D2 gastrectomy in Europe.

To improve the quality of D2 lymphadenectomy, a dedicated project was launched by expert surgeons belonging to the European Chapter of the International Gastric Cancer Association (IGCA). A questionnaire has been designed to ask participant surgeons the planned

extent of lymphadenectomy, i.e., which nodal stations (Fig. 2) should be removed in specified clinical scenarios (Table 3). This is intended to determine the definition of D2 lymphadenectomy across Europe as well as the indications and possible variations of D2 procedures according to depth of tumour invasion, presence of positive lymph nodes, tumour site, and histology.

In addition, a datasheet has been created (Fig. 3), to collect data retrospectively on the total number of resected nodes, and the total number of positive nodes for cases consecutively treated by each of the participants from January to December 2014. For centres with available data, the number of retrieved and positive lymph nodes for each nodal station and the intended extent of lymph-node dissection will be collected.

## Conclusion

There is a large variability in the number of retrieved nodes after D2 dissection in European series. This reflects, at least partly, different approaches to D2 lymphadenectomy by European surgeons and may be responsible of the different outcomes observed in patients with gastric cancer across Europe. Therefore, there is the need to standardize the practice of D2 gastrectomy in Europe and to define

**Table 3** D2 Audit questionnaire by the European Chapter of International Gastric Cancer Association

1	cT1 N0 gastric adenocarcinoma located in the gastric antrum
2	cT1N0 with intestinal Laurèn type located in the middle-upper part of the stomach
3	cT1N0 cardia Siewert type III adenocarcinoma
4	cT1 N+ gastric adenocarcinoma with intestinal Laurèn histology located in the middle-upper part of the stomach
5	cT1 N0 gastric adenocarcinoma with diffuse Laurèn histology located in the the middle-upper part of the stomach
6	cT1 N+ gastric adenocarcinoma located in the middle-upper part of the stomach in a high-morbidity patient with Charlson Comorbidity Score (CCS) >5
7	cT2-T3 N0 gastric adenocarcinoma located in gastric antrum
8	cT2-T3 N+ gastric adenocarcinoma located in gastric antrum
9	cT2-T3 N0 gastric adenocarcinoma located in gastric body along the greater curvature. In the previous case would you perform a splenectomy?  <input type="checkbox"/> Yes <input type="checkbox"/> Not
10	cT2-T3 N+ gastric adenocarcinoma located in gastric body along the greater curvature with positive lymphnodes at the splenic hilum. In the previous case would you perform a splenectomy?  <input type="checkbox"/> Yes <input type="checkbox"/> Not
11	cT4a N+ gastric adenocarcinoma with intestinal hystology located in gastric antrum.
12	cT4a N+ gastric adenocarcinoma with diffuse Laurèn hystology located in gastric antrum.
13	cT4a N+ gastric adenocarcinoma with intestinal hystology located in gastric body along the greater curvature. In the previous case would you perform a splenectomy?  <input type="checkbox"/> Yes <input type="checkbox"/> Not
14	gastric <i>linitis plastica</i> .
15	At your hospital do you perform splenectomy:  <input type="checkbox"/> Routinely during D2 procedures <input type="checkbox"/> In cases of positive lymphnodes at splenic hilum to perform a complete lymphadenectomy <input type="checkbox"/> Only in cases of direct invasion of the spleen by the primary tumour or positive lymphnodes
16	At your hospital do you perform distal pancreatectomy:  <input type="checkbox"/> Routinely during D2 procedures <input type="checkbox"/> Only in cases of direct invasion of the pancreas by the primary tumour or positive nodes
17	Do you extend lymphadenectomy for gastric cancer beyond the D2 dissection?  <input type="checkbox"/> Yes <input type="checkbox"/> Not  If yes, please describe the indications to lymphadenectomy extended beyond the D2 dissection and which are the nodal stations removed.
18	Do you usually dissect the surgical specimen after gastrectomy to separately send the removed lymph nodes for the pathological examination in numbered containers corresponding to the numerical system for lymph node identification reported by the Japanese Research Society for the study of Gastric Cancer?  <input type="checkbox"/> Yes <input type="checkbox"/> Not
19	Do you usually record in a database the number of retrieved lymph nodes and the number of metastatic lymph nodes per each nodal station?  <input type="checkbox"/> Yes <input type="checkbox"/> Not  If yes, please fill in the attached file with the information regarding patients treated between January and December 2014.

Questions from 1 to 14 report specific clinical scenarios: the surgeons joining the project should mark which nodal stations would be removed in each clinical scenario using the electronic form, as showed in Fig. 2. For the question 19, each participant should record in a database (Fig. 3), the number of retrieved lymph nodes, and the number of metastatic lymph nodes for each nodal station of patients treated in 2014

**Fig. 3** D2 Audit datasheet to collect data retrospectively on the total number of resected nodes, and the total number of positive nodes for cases consecutively treated by each of the participants from Janu-

ary to December 2014. For centres with available data, the number of retrieved and positive lymph nodes for each nodal station and the intended extent of lymph-node dissection will be also collected

possible variations of D2 procedures according to tumour's characteristics.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Research involving human participants and/or animals** The research does not involve human participants and/or animals.

**Informed consent** There was no need to get informed consent.

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