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## Problems faced by evidence-based medicine in evaluating lymphadenectomy for gastric cancer

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### Abstract

Gastric cancer surgical management differs between Eastern Asia and Western countries. Extended lymphadenectomy (D2) is the standard of care in Japan and South Korea since decades, while the majority of United States patients receive at most a limited lymphadenectomy (D1). United States and Northern Europe are considered the scientific leaders in medicine and evidence-based procedures are the cornerstone of their clinical practice. However, surgeons in Eastern Asia are more experienced, as there are more new cases of gastric cancer in Japan (107898 in 2012) than in the entire European Union (81592), or in South Korea (31269) than in the entire United States (21155). For quite a long time evidence-based medicine (EBM) did not solve the question whether D2 improves long-term prognosis with respect to D1. Indeed, eastern surgeons were reluctant to perform D1 even in the frame of a clinical trial, as their patients had a very good prognosis after D2. Evidence-based surgical indications provided by Western trials were questioned, as surgical procedures could not be properly standardized. In the present study

we analyzed indications about the optimal extension of lymphadenectomy in gastric cancer according to current scientific literature (2008-2012) and surgical guidelines. We searched PubMed for papers using the key words "lymphadenectomy or D1 or D2" AND "gastric cancer" from 2008 to 2012. Moreover, we reviewed national guidelines for gastric cancer management. The support to D2 lymphadenectomy increased progressively from 2008 to 2012: since 2010 papers supporting D2 have achieved a higher overall impact factor than the other papers. Till 2011, D2 was the procedure of choice according to experts' opinion, while three meta-analyses found no survival advantage after D2 with respect to D1. In 2012-2013, however, two meta-analyses reported that D2 improves prognosis with respect to D1. D2 lymphadenectomy was proposed as the standard of care for advanced gastric cancer by Japanese National Guidelines since 1981 and was adopted as the standard procedure by the Italian Research Group for Gastric Cancer since the Nineties. D2 is now indicated as the standard of surgical treatment with curative intent by the German, British and ESMO-ESSO-ESTRO guidelines. At variance American NCCN guidelines recommend a D1<sup>+</sup> or a modified D2 lymph node dissection. In conclusion, D2 lymphadenectomy, originally developed by Eastern surgeons, is now becoming the procedure of choice also in the West. In gastric cancer surgery EBM is lagging behind national guidelines, rather than preceding and orienting them. To eliminate this lag, EBM should value to a larger extent Eastern Asian literature and should evaluate not only the quality of the study design but also the quality of surgical procedures.

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**Key words:** Gastric cancer; Surgical quality; Lymphadenectomy; Evidence-based medicine; National guidelines; Eastern Asia; United States

**Core tip:** The extension of lymphadenectomy in advanced gastric cancer has been debated for several

decades. Till recently Western surgeons supported limited lymphadenectomy in agreement with a Cochrane review and several meta-analyses, while Japanese surgeons preferred the extended procedure. Nowadays extended lymphadenectomy is considered the procedure of choice by most national guidelines. In gastric cancer surgery evidence-based medicine (EBM) is lagging behind national guidelines, rather than preceding and orienting them. To eliminate this lag, EBM should value to a larger extent Eastern Asian literature and should evaluate not only the quality of the study design but also the quality of surgical procedures.

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## HISTORICAL PERSPECTIVE

### **Eastern-Western discrepancies in gastric cancer surgery**

Gastric cancer surgery differs between Eastern Asia and the United States. Extended lymphadenectomy (D2) has been the standard of care for advanced gastric cancer in Japan and South Korea since decades<sup>[1-3]</sup>, while the majority of patients in the United States receive at most a limited lymphadenectomy (D1) followed by post-operative chemoradiation<sup>[4]</sup>. This difference is even more striking, if one considers that Japanese surgeons had extended lymphadenectomy to para-aortic nodes (D3 procedure), until a randomized controlled trial showed no survival advantage with respect to D2 procedure<sup>[5]</sup>. On the contrary, in the United States less than a D1 lymphadenectomy has been performed in a substantial proportion, or even in the majority of patients such as in the Intergroup 0116 trial<sup>[6]</sup>.

### **Western countries are the leaders in medical research**

United States and Northern European countries are considered the scientific leaders in medicine: indeed the most important medical journals are published in the United States [*New Engl J Med*, impact factor (IF) in 2012 = 51.658; *Science*, IF = 31.027] or in England (*Lancet*, IF = 39.060; *Nature*, IF = 38.597).

Evidence-based procedures are the cornerstone of clinical practice in Western countries. Anyway, due to the difficulty in standardizing surgical procedures, evidence-based surgical indications may not be unquestionable. The extent of lymphadenectomy in surgical management of gastric cancer proves this point.

Indeed the Western surgical approach to advanced gastric cancer was supported by a Cochrane review published in 2003<sup>[7]</sup> and 2005<sup>[8]</sup>, reporting that “randomised studies show no evidence of overall survival benefit” after D2 dissection, “but possible benefit in T3 tumors.” These conclusions were mainly based on the results of a

Dutch<sup>[9]</sup> and a British<sup>[10]</sup> trials, showing that D2 provided no 5-year survival advantage with respect to D1. Of note, the Cochrane review acknowledged that “these results may be confounded by surgical learning curves and poor surgeon compliance”<sup>[8]</sup>.

However it was acknowledged that D2 lymphadenectomy was necessary to harvest at least 15 lymph nodes, *i.e.*, to adequately stage tumours<sup>[11,12]</sup>. To circumvent this problem, nodal invasion was evaluated not only by N status but also by N ratio<sup>[13,14]</sup>.

### **While eastern countries have the largest surgical experience**

On the other hand, surgeons in Eastern Asia are more experienced, as there are more new cases of gastric cancer in Japan (107898 in 2012) than in the 28 countries of the European Union (81592), or in South Korea (31269) than in the entire United States (21155)<sup>[15]</sup> (Figure 1).

Indeed Eastern surgeons achieve better short-term results than their Western counterparts (Table 1)<sup>[16]</sup>. Of note, the two trials on which the Cochrane review was based<sup>[17,18]</sup> had been carried out by surgeons without previous training in extended lymphadenectomy, doing less than 5 five interventions per year. The limited surgical experience yielded a very high post-operative mortality after extended lymphadenectomy (9.7% in the Dutch trial and 13.5% in the British trial), a high percentage of splenectomies (37% and 65%, respectively) and pancreatectomies (30% and 56%) and a low number of retrieved nodes (median of 17 nodes in the British trial)<sup>[19]</sup>. By comparison, at the same time, mortality after D2 dissection was less than 2% in the nationwide Japanese registry<sup>[20]</sup>; likewise in a Japanese trial mortality after D2 was less than 1% and the median number of retrieved nodes was 54<sup>[21]</sup>. Of note, in the Dutch trial D2 was associated with an increased long-term survival with respect to D1 when excluding post-operative mortality ( $P = 0.02$ )<sup>[22]</sup>.

In the meantime another randomized trial, performed in Taiwan<sup>[23]</sup>, showed a mild but significant survival advantage after D2 with respect to D1; 5-year survival was 59.5% and 53.6%, respectively ( $P = 0.041$ ); interestingly, none of the patients recruited died in the post-operative period<sup>[24]</sup>. Of note, a clinical trial comparing D1 and D2 could not be devised in Japan at that time, as the two procedures were not in equipoise according to Japanese surgeons. The Japan Clinical Oncology Group instead performed a trial to compare D2 and D3 lymphadenectomies<sup>[5]</sup>.

In the Eastern-Western debate on gastric cancer, the Eastern position is considerably strengthened by the impressive long-term survival of Eastern patients: overall 5-year survival achieved values of 68%-74% in Japanese gastric cancer patients<sup>[2,25]</sup> whereas in Europe during the 1990s survival was three-fold lower (24%)<sup>[26]</sup>.

### **Italian Research Group for Gastric Cancer between the East and the West**

Of note, the GIRCG (Gruppo Italiano per la Ricerca sul Cancro Gastrico-Italian Research Group for Gastric Cancer) gave an important contribution to the debate on the

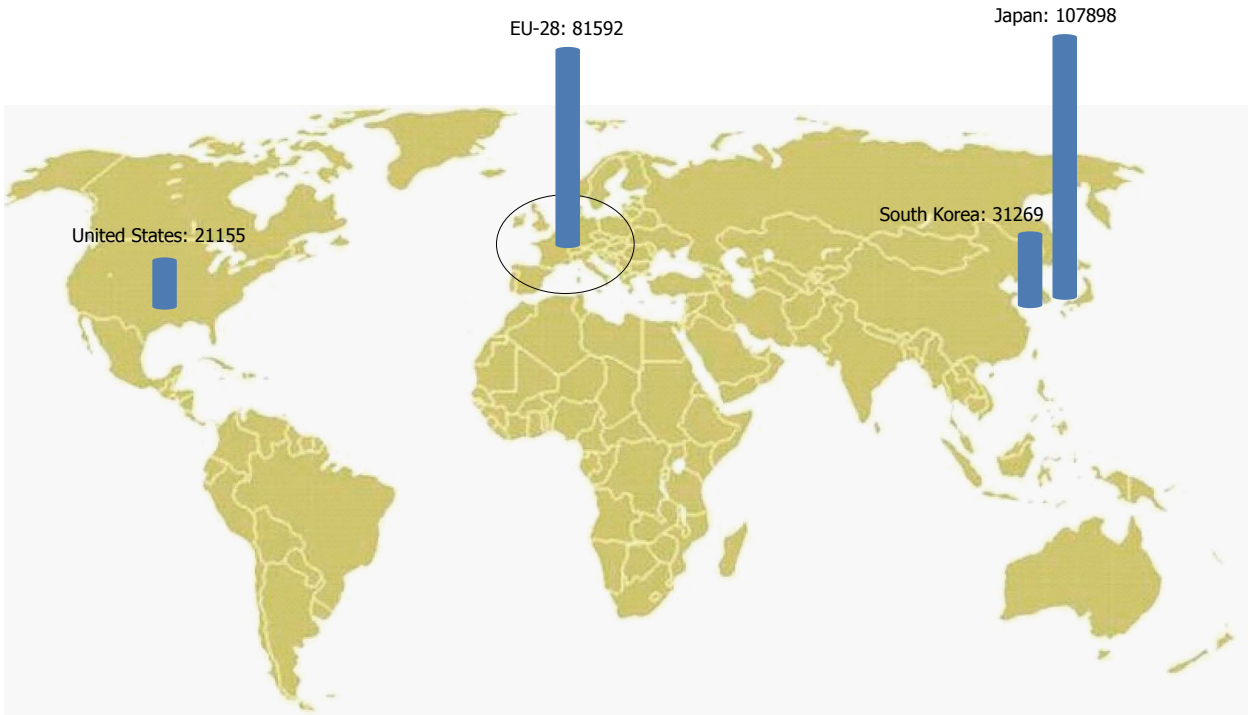


Figure 1 New cases of gastric cancer in 2012 in the West and in the East, according to GLOBOCAN 2012<sup>[15]</sup>.

**Table 1 Short-term results of gastric cancer surgery with D2 lymphadenectomy in Eastern Asia vs Europe, in clinical trials vs observational studies<sup>[16]</sup>**

	Post-operative mortality	Post-operative morbidity	Median nodes retrieved	Adequate staging (≥ 15 nodes)
Eastern Asia				
Trials	0%-0.8%	17%-21%	54	100%
Observational	< 2%	-	-	-
Europe				
Trials	5%-14%	43%-46%	17	-
Observational	2%-5%	21%-35%	25-26	86%-95%
IRGGC (VR, SL, PD)	3.6%	33.6%	29 (IQ 21-38)	93.8%

IRGGC: Italian Research Group for Gastric Cancer.

extension of lymphadenectomy for gastric cancer.

First of all the GIRCG showed that D2 dissection is feasible on western patients with acceptable mortality and morbidity (2% and 17% respectively) rates and provides 32% probability of 5-year survival, even for patients with involvement of regional lymph nodes<sup>[27]</sup>.

In 2005 De Manzoni and Verlato<sup>[28]</sup> criticized the Cochrane review on gastric cancer surgery<sup>[8]</sup> (later withdrawn<sup>[29]</sup>) for not taking into account the Japanese literature. Indeed in the past the British and American physicians gave a fundamental contribution to understanding even diseases which were rare in their countries: for instance, beta thalassemia was named Cooley's anemia after the American physician who first described the disease in immigrant Italian children with characteristic anemia and bone deformities<sup>[30]</sup>. However, nowadays scientific

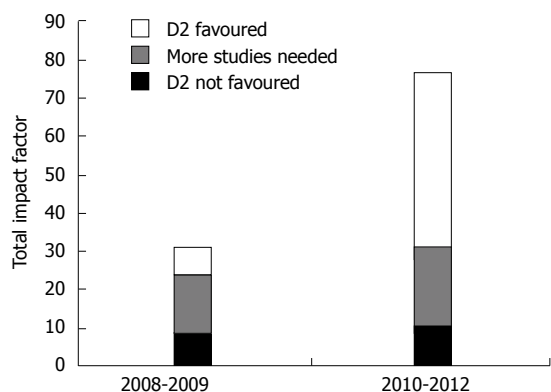
methodology has spread to several countries<sup>[31]</sup>, so that the leading countries in a particular medical field are often those with the highest incidence, such as Japan and South Korea for gastric cancer. Indeed "it is extremely difficult to ask Japanese surgeons, in whose series postoperative mortality is only 1%-2%, to believe in randomized clinical trials where postoperative mortality peaks to 10%-14%, irrespectively of methodological quality of those studies<sup>[16]</sup>.

In 2009 Verlato *et al*<sup>[16]</sup> pointed out that "in this third millennium, papers dealing with surgery for gastric cancer cannot be evaluated only according to the quality of the study design, such as the Jadad score, but also the quality of surgical procedures must be taken into account". To overcome this problem Verlato *et al*<sup>[16]</sup> proposed indexes of surgical quality (number of retrieved nodes, percentage of splenectomy and splenopancreasectomy, postoperative morbidity, and in-hospital mortality). Indeed, the learning curve, standardization of the procedures, poor surgical performances are among the main difficulties related to RCTs in the surgical field. Also randomization can be hampered by ethical issues, emergency setting, or need of palliative care, while patients' and surgeons' equipoise can be more difficult to achieve than in the medical field<sup>[32]</sup>.

## COMPARISON OF NATIONAL GUIDELINES AND CURRENT SCIENTIFIC RESEARCH

### Extension of lymphadenectomy recommended by national guidelines

D2 was adopted as the standard of surgical treatment with curative intent by the Japanese<sup>[1,2,25,33]</sup>, German<sup>[34,35]</sup>



**Figure 2 Overall Impact Factor of articles, classified as a function of D1/D2 preferences (D1 favoured, more studies needed, D2 favoured) and time (2008/09 vs 2010/12).**

and British<sup>[36]</sup> national guidelines, by the European Society for Medical Oncology (ESMO) guidelines<sup>[37]</sup>, by the joint ESMO - European Society of Surgical Oncology (ESSO) - European Society of Radiotherapy and Oncology (ESTRO) guidelines<sup>[38]</sup>. The ESMO-ESSO-ESTRO guidelines ranked the level of evidence as the highest (I) and the grade of recommendation as B (strong or moderate evidence for efficacy but with a limited clinical benefit)<sup>[38]</sup>. Of note, D2 is recommended by the Japanese guidelines since 1981<sup>[1]</sup> and by German guidelines since at least 2005<sup>[34]</sup>, and D2 was adopted as the preferred lymphadenectomy within the Italian Research Group for Gastric Cancer (GIRCG) since 1992<sup>[16,27]</sup>. At variance American NCCN guidelines recommend a D1+ or a modified D2 lymph node dissection, the latter performed by experienced surgeons in high-volume centers<sup>[39]</sup>.

### **Optimal extension of lymphadenectomy according to current scientific literature (2008-2012)**

We searched PubMed for papers using the key words “lymphadenectomy or D1 or D2” AND “gastric cancer”, published in English language between 2008 and 2012. The year 2013 was not included in the systematic review, as the articles published in this year were still being introduced in medical databases which are updated with some delay. The search was limited to full-length articles in English language. In addition, bibliographies were manually inspected, to identify the relevant publications for possible inclusion.

Potentially relevant studies ( $n = 1174$ ) were identified and screened for retrieval. Letters and commentaries were excluded; when duplicate articles on the same series were found, only the most recent was considered. A total of 45 full-length articles, comparing short and/or long-term effectiveness of either lymphadenectomies, were considered, 5 supporting D1, 25 supporting D2, and 15 underlying the need for further studies. Of these, 35 articles had been published on journals indexes by the Journal Citation Reports, 13 pointing out the need for further studies<sup>[40-52]</sup>, 5 favouring D1<sup>[53-57]</sup>, 17 supporting D2<sup>[58-74]</sup> (Table 2). Interestingly no article published on journals

without impact factor was in favour of D1 lymphadenectomy, while 8 supported D2<sup>[75-82]</sup> and 2 underlined the need for more studies<sup>[83-84]</sup>.

As shown in Figure 2 and in Table 2<sup>[40-74]</sup>, the support to D2 lymphadenectomy increased progressively during the study period: since 2010 papers supporting D2 have achieved a higher overall IF than the other papers.

Initially D2 was indicated as the procedure of choice mainly by review articles and papers conveying expert opinion, while three meta-analyses<sup>[53,55,56]</sup>, published between 2008 and 2011, reported that extended lymphadenectomy does not offer benefit over limited lymphadenectomy. However, in 2012 D2 was indicated as the procedure of choice in advanced gastric cancer also by a meta-analysis<sup>[73]</sup>. “Earlier trials show that D2 dissections have higher operative mortality, while recent trials have similar rates. A trend of improved survival exists among D2 patients who did not undergo resection of the spleen or pancreas, as well as for patients with T3/T4 cancers”<sup>[73]</sup>.

Also the authors of the Dutch trial, after considering the 15-year follow-up results, concluded that: “Considering that a safer, spleen-preserving D2 resection is currently available in high-volume centres, and our findings of better recurrence and gastric-cancer-related survival rates, D2 resection now seems likely to be the recommended surgical approach for patients with resectable (curable) gastric cancer, despite the earlier follow-up results”<sup>[65]</sup>.

The authors of another clinical trial performed in Italy<sup>[47]</sup> reported that patients undergoing D1 or D2 experienced similar post-operative morbidity (12% and 17.9% respectively) and mortality (3% and 2.2%) and concluded that “D2 dissection, in an appropriate setting, can therefore be considered a safe option for the radical management of gastric cancer in Western patients”.

In the era of tailored treatment, other Authors suggested to move “away from the D2 versus D1 debate” and to choose the extension of lymphadenectomy according to “the stage of the cancer and the age and fitness of the patient”<sup>[85]</sup>. Similarly, an expert panel, using the RAND/UCLA appropriateness methodology, concluded that “a D2 lymphadenectomy is preferred for curative-intent resection in advanced, nonmetastatic GC; and in patients with early GC or substantial comorbidities, a D1 lymphadenectomy is more appropriate”<sup>[86]</sup>.

## **CONCLUSION**

### **Towards an international agreement?**

EBM, which till recently has not reported any advantage of extended D2 lymphadenectomy with respect to the limited D1 procedure<sup>[7,8,53,55,56]</sup>, is now supporting D2. A clinical trial performed in the East highlighted a significant 5-year survival advantage after D2 with respect to D1<sup>[23]</sup>. A clinical trial performed on Western patients showed that D2 can be performed without excess post-operative morbidity or mortality<sup>[47]</sup>. The most recent meta-analyses<sup>[73,87]</sup> concluded that “D2 lymphadenectomy with spleen and pancreas preservation offers the most survival benefit”<sup>[87]</sup>

**Table 2 Summary of the systematic review of studies, comparing limited (D1) and extended (D2) lymphadenectomy and published in 2008-2012 on journals indexed by Journal Citation Reports. Articles were weighted according to 5-year impact factor (2008-2012)**

Authors	Country	Journal	Year	Study design	5-yr IF
Further studies	Further studies needed				
Catalano <i>et al</i> <sup>[40]</sup>	Italy	<i>Crit Rev Oncol Hematol</i>	2009	Expert opinion	4.562
Coburn <sup>[41]</sup>	Canada	<i>J Surg Oncol</i>	2009	Review	2.710
D'souza <i>et al</i> <sup>[42]</sup>	India	<i>J Cancer Res Ther</i>	2009	Review	0.761 <sup>1</sup>
Songun <i>et al</i> <sup>[43]</sup>	The Netherlands	<i>Expert Rev Anticanc</i>	2009	Expert opinion	2.055
Yoon <i>et al</i> <sup>[44]</sup>	United States	<i>Oncologist</i>	2009	Expert opinion	5.245
Coburn <sup>[45]</sup>	Canada	<i>J Surg Oncol</i>	2010	Expert opinion	2.710
de Bree <i>et al</i> <sup>[46]</sup>	Greece	<i>J Surg Oncol</i>	2010	Review	2.710
Degiuli <i>et al</i> <sup>[47]</sup>	Italy	<i>Brit J Surg</i>	2010	Clinical trial	4.956
Tanizawa <i>et al</i> <sup>[48]</sup>	Japan	<i>Gastric Cancer</i>	2010	Review	3.615
Maduekwe <i>et al</i> <sup>[49]</sup>	United States	<i>J Gastrointest Surg</i>	2011	Review	2.766
Doglietto <i>et al</i> <sup>[50]</sup>	Italy	<i>Ann Ital Chir</i>	2012	Expert opinion	0.286
Hundahl <sup>[51]</sup>	United States	<i>Surg Oncol Clin N Am</i>	2012	Review	1.162
Vallbohmer <i>et al</i> <sup>[52]</sup>	Germany	<i>Curr Prob Surg</i>	2012	Expert opinion	2.267
Overall					35.805
D2 not favoured	D2 not favoured over D1				
Lustosa <i>et al</i> <sup>[53]</sup>	Brazil	<i>Acta Cir Bras</i>	2008	Meta-analysis	0.695
Van Cutsem <i>et al</i> <sup>[54]</sup>	EORTC <sup>2</sup>	<i>Eur J Cancer</i>	2008	Expert opinion	5.257
Yang <i>et al</i> <sup>[55]</sup>	China	<i>Am J Surg</i>	2009	Meta-analysis	2.727
Memon <i>et al</i> <sup>[56]</sup>	Australia	<i>Ann Surg</i>	2011	Meta-analysis	8.264
Wong <i>et al</i> <sup>[57]</sup>	United States	<i>Curr Treat Option On</i>	2011	Expert opinion	2.422 <sup>1</sup>
Overall					19.365
D2 favoured	D2 favoured over D1				
Ozmen <i>et al</i> <sup>[58]</sup>	Turkey	<i>J Surg Oncol</i>	2008	Review	2.710
Díaz de Liaño <i>et al</i> <sup>[59]</sup>	Spain	<i>Clin Transl Oncol</i>	2009	Observational	1.316
Griniatsos <i>et al</i> <sup>[60]</sup>	Greece	<i>World J Gastroenterol</i>	2009	Observational	2.594
Kodera <i>et al</i> <sup>[61]</sup>	Japan	<i>Acta Chir Belg</i>	2009	Review	0.499
Roy <i>et al</i> <sup>[62]</sup>	India	<i>Indian J Surg</i>	2009	Review	0.092 <sup>1</sup>
Sasako <i>et al</i> <sup>[63]</sup>	Japan	<i>Jpn J Clin Oncol</i>	2010	Expert opinion	2.063
Shi <i>et al</i> <sup>[64]</sup>	China	<i>J Surg Oncol</i>	2010	Review	2.710
Songun <i>et al</i> <sup>[65]</sup>	The Netherlands	<i>Lancet Oncol</i>	2010	Clinical trial	21.856
Tentes <i>et al</i> <sup>[66]</sup>	Greece	<i>J BUON</i>	2010	Observational	0.653
Hussain <sup>[67]</sup>	United Kingdom	<i>Curr Opin Gastroen</i>	2011	Expert opinion	3.739
Meyer <i>et al</i> <sup>[68]</sup>	Germany	<i>Dtsch Arztebl Int</i>	2011	Expert opinion	2.988
Ott <i>et al</i> <sup>[69]</sup>	Germany	<i>Langenbecks Arch Surg</i>	2011	Review	1.970
Saka <i>et al</i> <sup>[70]</sup>	Japan	<i>Jpn J Clin Oncol</i>	2011	Review	2.063
Lee <i>et al</i> <sup>[71]</sup>	Korea	<i>Yonsei Med J</i>	2012	Review	1.214
Sasako <sup>[72]</sup>	Japan	<i>Surg Oncol Clin N Am</i>	2012	Expert opinion	1.162
Seevaratnam <i>et al</i> <sup>[73]</sup>	Canada	<i>Gastric Cancer</i>	2012	Meta-analysis	3.615
Viudez-Berral <i>et al</i> <sup>[74]</sup>	Spain	<i>Rev Esp Enferm Dig</i>	2012	Expert opinion	1.208
Overall					52.452

<sup>1</sup>2012 impact factor was used, as the 5-year impact factor was not available; <sup>2</sup>EORTC: European Organisation for Research and Treatment of Cancer.

for patients with advanced gastric cancer.

The latest American guidelines<sup>[39]</sup> now include not only D1+ but also “a modified D2 lymph node dissection” among recommended procedures for patients with resectable locoregional cancer, as long as the latter is “performed by experienced surgeons in high-volume centers”.

Two American authors<sup>[88]</sup> recently underlined that Eastern and Western surgeons are converging to consider D2 lymphadenectomy as the standard procedure, as the former have given up with super-extended procedures, while the latter “have increasingly accepted the importance of performing more than a D1 node dissection”.

### Problems of EBM in gastric cancer surgery and possible solutions

In gastric cancer surgery EBM is lagging behind national

guidelines, rather than preceding and orienting them. To eliminate this lag, EBM should value to a larger extent Eastern Asian literature<sup>[28]</sup> and should take into account not only the quality of the study design but also the quality of surgical procedures<sup>[16]</sup>.

In Western countries, where the incidence of gastric cancer is getting low, centralization of gastric cancer surgery in specialized high-volume institution would also be necessary.

As pointed out by Strong and Yoon<sup>[88]</sup> one significant obstacle to implementing D2 lymphadenectomy in the West is the low volume of gastrectomies in Western centres. Indeed in the United States 80% of Medicare patients undergo gastrectomy in centers performing less than 20 procedures per year<sup>[89]</sup>. This situation reflects not only the low incidence of gastric cancer in the United States but also the surgeon's habit to consider gastric sur-

gery as part of general surgery<sup>[88]</sup>.

However, several Northern European countries managed to achieve great improvements in gastric cancer surgery at national level. In the Netherlands survival of gastric cancer patients significantly improved after the implementation of the Dutch D1-D2 Gastric Cancer Trial, which involved substantial standardization and training<sup>[90]</sup>. In Denmark 30-d hospital mortality has decreased from 8.2% to 2.4% after centralization of gastric cancer surgery and implementation of national clinical guidelines while the proportion of patients with at least 15 lymph nodes removed has increased from 19% to 76%<sup>[91]</sup>. Centralization of gastric cancer surgery and/or audits for gastric cancer are currently implemented in the United Kingdom, Sweden, Finland, and the Netherlands<sup>[92,93]</sup>.

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