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TOPIC HIGHLIGHT

2016 Gastric Cancer: Global view

Gastric cancer: Current status of lymph node dissection

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Abstract

D2 procedure has been accepted in Far East as the standard treatment for both early (EGC) and advanced gastric cancer (AGC) for many decades. Recently EGC has been successfully treated with endoscopy by endoscopic mucosal resection or endoscopic submucosal dissection, when restricted or extended Gotoda's criteria can be applied and D1+ surgery is offered only to patients not fitted for less invasive treatment. Furthermore, two randomised controlled trials (RCTs) have been demonstrating the non inferiority of minimally invasive technique as compared to standard open surgery for the treatment of early cases and recently the feasibility of adequate D1+ dissection has been demonstrated also for the robot assisted technique. In case of AGC the debate on the extent of nodal dissection has been open for many decades. While D2 gastrectomy was performed as the standard procedure in eastern countries, mostly based on observational and retrospective studies, in the west the

Medical Research Council (MRC), Dutch and Italian RCTs have been conducted to show a survival benefit of D2 over D1 with evidence based medicine. Unfortunately both the MRC and the Dutch trials failed to show a survival benefit after the D2 procedure, mostly due to the significant increase of postoperative morbidity and mortality, which was referred to splenopancreatectomy. Only 15 years after the conclusion of its accrual, the Dutch trial could report a significant decrease of recurrence after D2 procedure. Recently the long term survival analysis of the Italian RCT could demonstrate a benefit for patients with positive nodes treated with D2 gastrectomy without splenopancreatectomy. As nowadays also in western countries D2 procedure can be done safely with pancreas preserving technique and without preventive splenectomy, it has been suggested in several national guidelines as the recommended procedure for patients with AGC.

Key words: Gastric cancer; Lymph node dissection; Lymphadenectomy; D2 gastrectomy; D1 gastrectomy; D1 plus gastrectomy; Robot assisted lymphadenectomy; Laparoscopic lymphadenectomy

Core tip: Recently early gastric cancer and advanced gastric cancer (AGC) has been successfully treated endoscopically; surgery is offered only to patients not fitted for less invasive treatment and in several guidelines D1+ (open, laparoscopic, robotic) is the adequate treatment. For AGC, while D2 gastrectomy is the standard procedure in eastern countries, mostly based on retrospective studies, in the west different randomised controlled trials have been conducted to demonstrate a survival benefit of D2 over D1 with evidence based medicine, with contradictory results. As nowadays D2 gastrectomy can be done safely with pancreas and spleen preservation, it has been suggested also in several western guidelines as the recommended procedure for patients with AGC.

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INTRODUCTION

The Japanese Research Society for Gastric Cancer (JRSGC) published the first edition of the General Rules for Gastric Cancer Study in 1973[1]. In fact, several lymph node studies performed in the 50's and 60' in Japan revealed pathways of lymph node drainage. Following these studies, in the first English edition of the General Rules of JRSGC[2], which were widely accepted and adopted in many countries, regional lymph nodes were classified into 16 stations by their location (Table 1, Figure 1A).

In 1997, the JRSGC was transformed into the Japanese Gastric Cancer Association and this new association has maintained its commitment to the concept of the Japanese Classification. The aim of this classification is to provide a common language for the clinical and pathological description of gastric cancer. In the newest classification of the Japanese Gastric Cancer Association (JGCA), there is a very comprehensive description of regional lymph node, as follow[3].

Anatomical definition of lymph nodes and lymph node regions

The regional lymph nodes of the stomach are classified into stations numbered as in Table 2, from 1 to 20, plus stations 110, 111 and 112. Some of lymph node stations numbered from 1 to 20 have been subdivided in further subsets of nodes (Figure 1B and C). Lymph node stations 1-12 and LN station 14v are defined as regional stations; the remnant lymph node stations are considered as distant stations and metastases to these nodes are classified as M1. Lymph nodes No. 19, 10, 110 and 111 are considered as regional lymph nodes in case of tumor invading the esophagus.

Lymph node metastasis (N) are classified as follows: (1) NX: regional lymph nodes cannot be assessed; (2) N0: no regional lymph nodes metastasis; (3) N1: metastasis in 1-2 regional lymph nodes; (4) N2: metastasis in 3-6 regional lymph nodes; and (5) N3: metastasis in 7 or more regional lymph nodes; N3a, metastasis in 7-15 regional lymph nodes; N3b, metastasis in > 15 regional lymph nodes. In 2011 the JGCA published the Japanese gastric cancer treatment guidelines 2010 (ver. 3)[4] based on the 3rd English edition of the Japanese Classification of Gastric Carcinoma[3], which defined the extent of systematic lymphadenectomy according to the type (distal or total) of gastrectomy indicated. These guidelines report which lymph node stations are expected to be removed to perform a correct D1, D1+ or D2 in case of both distal and total gastrectomy (see chapter "definition of different levels of lymph node dissection).

ANATOMICAL BORDERS OF LOCO-REGIONAL LYMPH NODES

The strategy of lymph node dissection is based on a perfect knowledge of the anatomy of the upper abdominal vessels, which are usefull landmarks in the operating fields.

We will describe systematically all the locoregional lymph node stations, with particular regards to their anatomical and vascular borders.

Table 1 Numbering of lymph nodes according to the old classification of Japanese Research Society for Gastric Cancer (1962)

Station nr		Station nr	
1	Right cardiac nodes	9	Nodes around the coeliac axis
2	Left cardiac nodes	10	Nodes at the splenic hilus
3	Nodes along the lesser curvature	11	Nodes along the splenic artery
4	Nodes along the greater curvature	12	Nodes in the hepatoduodenal ligament
5	Suprapyloric nodes	13	Nodes at the posterior aspect of the pancreas head
6	Infrapyloric nodes	14	Nodes at the root of the mesenterium
7	Nodes along the left gastric artery	15	Nodes in the mesocolon of the transverse colon
8	Nodes along the common hepatic artery	16	Para-aortic lymph nodes

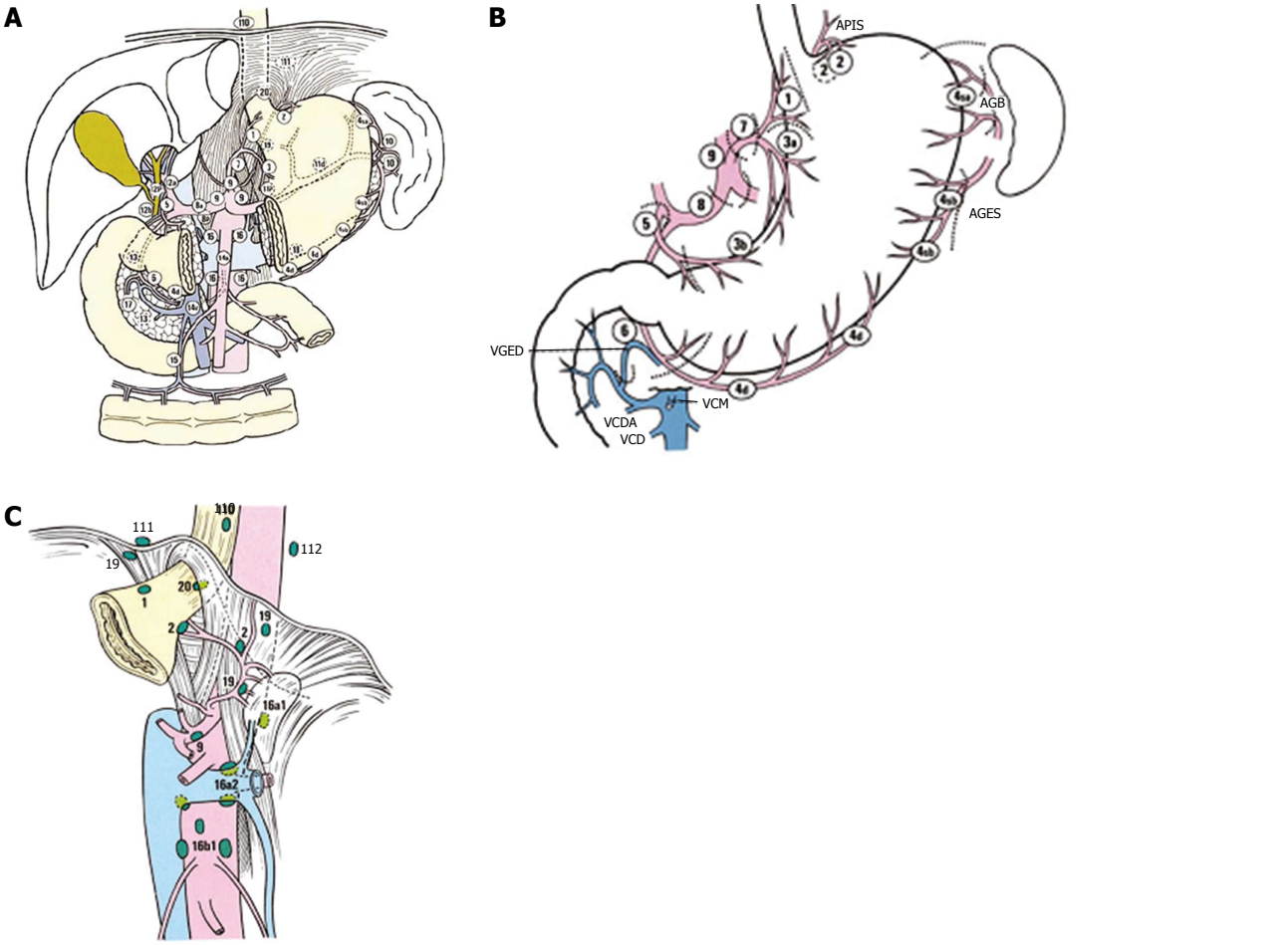

Figure 1 Locations of lymph node station. A: Numbering and locations of lymph node station according to the first edition of the General Rules of the JRSGC; B: Location of lymph node stations in the posterior area; C: Location of lymph node stations in subphrenic area. JRSGC: Japanese Research Society for Gastric Cancer; APIS: Arteria phrenica inferior sinistra; AGB: Arteriae gastricae breves; AGES: Arteria gastroepiploica sinistra; VGED: Vena gastroepiploica dextra; VCDA: Vena colica dextra accessoria; VCM: Vena colica media; VCD: Vena colica dextra.

Location number 1 (right paracardial nodes)

Perigastric lymph nodes on the right side of the cardia; they are located along the cardio-esophageal branch of the left gastric artery, from its origin from the left gastric artery to the oesophageal hiatus.

Location number 2 (left paracardial nodes)

Perigastric lymph nodes on the left side of the cardias, located along the cardio-oesophageal branch of the left inferior phrenic artery.

Location number 3 (lesser curvature nodes)

Perigastric lymph nodes at the lesser curvature, located along the inferior (descending) branch of the left gastric artery and along the right gastric artery distal to the first gastric branch.

Location number 4 (greater curvature nodes)

Perigastric lymph nodes at the greater curvature. This lymph node station is divided into a left (4s) and right (4d) part defined by the Von Ghoete point (the

Table 2 Anatomical definitions of lymph node stations

Nr.	Definition
1	Right paracardial LNs, including those along the first branch of the ascending limb of the left gastric artery
2	Left paracardial LNs including those along the esophagocardiac branch of the left subphrenic artery
3a	Lesser curvature LNs along the branches of the left gastric artery
3b	Lesser curvature LNs along the 2nd branch and distal part of the right gastric artery
4sa	Left greater curvature LNs along the short gastric arteries (perigastric area)
4sb	Left greater curvature LNs along the left gastroepiploic artery (perigastric area)
4d	Rt. greater curvature LNs along the 2nd branch and distal part of the right gastroepiploic artery
5	Suprapyloric LNs along the 1st branch and proximal part of the right gastric artery
6	Infrapyloric LNs along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreatoduodenal vein
7	LNs along the trunk of left gastric artery between its root and the origin of its ascending branch
8a	Anterosuperior LNs along the common hepatic artery
8p	Posterior LNs along the common hepatic artery
9	Coeliac artery
10	Splenic hilar LNs including those adjacent to the splenic artery distal to the pancreatic tail, and those on the roots of the short gastric arteries and those along the left gastroepiploic artery proximal to its 1st gastric branch
11p	Proximal splenic artery LNs from its origin to halfway between its origin and the pancreatic tail end
11d	Distal splenic artery LNs from halfway between its origin and the pancreatic tail end to the end of the pancreatic tail
12a	Hepatoduodenal ligament LNs along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas
12b	Hepatoduodenal ligament LNs along the bile duct, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas
12p	Hepatoduodenal ligament LNs along the portal vein in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas
13	LNs on the posterior surface of the pancreatic head cranial to the duodenal papilla
14v	LNs along the superior mesenteric vein
15	LNs along the middle colic vessels
16a1	Paraaortic LNs in the diaphragmatic aortic hiatus
16a2	Paraaortic LNs between the upper margin of the origin of the celiac artery and the lower border of the left renal vein
16b1	Paraaortic LNs between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery
16b2	Paraaortic LNs between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation
17	LNs on the anterior surface of the pancreatic head beneath the pancreatic sheath
18	LNs along the inferior border of the pancreatic body
19	Infradiaphragmatic LNs predominantly along the subphrenic artery
20	Paraesophageal LNs in the diaphragmatic esophageal hiatus
110	Paraesophageal LNs in the lower thorax
111	Supradiaphragmatic LNs separate from the esophagus
112	Posterior mediastinal LNs separate from the esophagus and the esophageal hiatus

LNs: Lymph nodes.

point where right and left gastropepiploic arteries meet each other at full channel). Furthermore the left part is divided into a proximal (4sa) and a distal part (4sb). Lymph nodes of the proximal part of left group 4 (4sa) are located around the short gastric arteries while lymph nodes of the distal part (4sb) are located along the left gastroepiploic artery. Lymph nodes of the right part of group 4 are located along the right gastroepiploic artery, distal to the first gastric branch.

Location number 5 (suprapyloric nodes)

Perigastric lymph nodes at the lesser curvature, located at the origin of the right gastric artery including its first gastric branch.

Location number 6 (infrapyloric nodes)

Perigastric lymph nodes at the greater curvature of the pylorus, located along the right gastroepipolic vessels from their origin from the gastroduodenal vessels till their first branches directed to the gastric wall.

Location number 7 (left gastric artery nodes)

Second tier lymph nodes located along the left gastric artery, from its origin from the coeliac trunk till its bifurcation into the cardioesophageal (ascending) and lower (descending) branches on the lesser curvature.

Location number 8 (common hepatic artery nodes)

Second tier nodes located around the common hepatic artery from its origin from the coeliac trunk to the branching off of the gastroduodenal artery. These lymph nodes are divided into an anterior part, 8a, and a posterior part, 8p (Figure 2).

Location number 9 (coeliac trunk nodes)

Second tier lymph nodes located around at the celiac axis including the origins of the common hepatic artery and splenic artery (Figure 2).

Location number 10 (splenic hilum nodes)

Second or third tier, or M lymph nodes, located at the

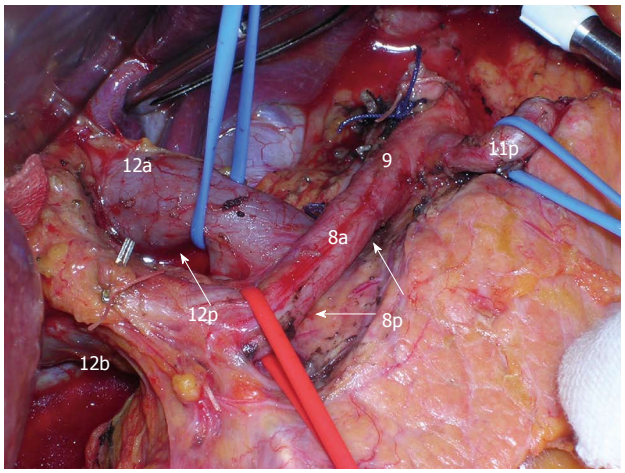

Figure 2 Complete lymph node removal along the hepatic pedicle (lymph node station nr 12a, 12b and 12p), common hepatic artery (lymph node station nr 8a and 8p), splenic artery (lymph node station nr 11p), coeliac axis (lymph node station nr 9).

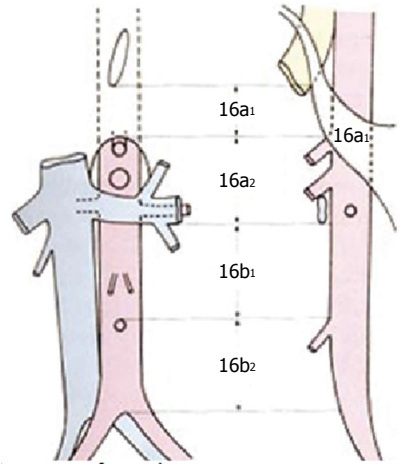

Figure 3 Anatomical borders of lymph node station nr 16.

splenic hilus, distal to the tip of the pancreas tail. At the lower pole of the spleen, the first gastric branch of the left gastroepiploic artery defines the vascular border between 10 and 4sb lymph nodes.

Location number 11 (splenic artery nodes)

Second tier nodes located along the splenic artery. These nodes have been divided into a proximal part, 11p, located around the splenic artery, from its origin from the celiac axis, till the branching off of the posterior gastric artery; and into a distal part, 11d, located around the splenic artery from the branching off of the posterior gastric artery to the tip of the pancreas tail (Figure 2).

Location number 12 (hepatoduodenal ligament nodes)

Second and third tier nodes (according to the site of the primary tumor) at the hepatoduodenal ligament. These nodes have been divided into 3 parts: left hepatoduodenal ligament nodes (12a), located at the left side of the proper hepatic artery; and posterior hepatoduodenal ligament nodes (12b and 12p), again divided into nodes located at the right and posterior side of the common hepatic duct (12b) and into nodes located posteriorly to the portal vein (12p) (Figure 2).

Location number 13 (retropancreatic nodes)

Third tier and M nodes, (according to the site of the primary tumor), along the superior and inferior branches of the posterior pancreaticoduodenal artery, located over the posterior side of the pancreas head. The left lateral border of this location is marked by the portal vein, while the upper border is represented by the origin of locations 12b and 12p.

Location number 14 (superior mesenteric vein and artery nodes)

Second and third tier and M nodes (according to the site of the primary tumor) along the origin of the superior mesenteric vein (VMS) (14 v) and M nodes along the origin of the superior mesenteric artery (AMS), at the root of the mesenterium. The lateral border is represented by the branching of the gastrocolic vein (TGC); the lower border is located at the branching off of the middle colic vein from the VMS and the upper border is represented by the origin of the AMS at the lower hedge of the pancreas.

Location number 15 (middle colic nodes)

M nodes located in the transverse mesocolon around the middle colic vessels, from their origin from the superior mesenteric vessels, till the mesocolic hedge of the transverse colon.

Location number 16 (aortic hiatus -a1, middle -a2/b1 and caudal -b2 paraaortic nodes)

Location number 16 includes in fact 4 separate groups of lymph nodes. All of them are nodes around the abdominal aorta and inferior vena cava. The groups are the following: 16a1, M nodes around the aortic hiatus, over the anterior side of the aorta, from the inferior hedge of the hiatus to the upper border of the coeliac trunk; 16a2, M nodes located over the anterior side of the aorta, from the coeliac trunk to the lower hedge of the left renal vein; 16b1, third tier nodes located around the anterior face of the aorta and vena cava, from the lower hedge of the left renal vein to the upper border of the inferior mesenteric artery; right and left border are defined by the right hedge of the inferior vena cava and by the left ovarian (spermatic) vessels; 16b2, M nodes located around the anterior face of the aorta and vena cava, from the upper border of the inferior mesenteric artery to the aortic bifurcation (Figure 3).

DEFINITIONS OF DIFFERENT LEVELS OF LYMPH NODE DISSECTION

In the Japanese gastric cancer treatment guidelines

2010 (ver. 3) based on the 3rd English edition of the Japanese Classification of Gastric Carcinoma, the JGCA defined the extent of systematic lymphadenectomy according to the type of gastrectomy indicated[4].

For total gastrectomy, the lymph nodes stations to be dissected in D1 lymphadenectomy are stations from No.1 to 7; D1+ includes D1 stations plus stations No.8a, 9, and 11p, and D2 includes D1 stations plus stations No.8a, 9, 10, 11p, 11d, and 12a. For tumors invading the esophagus, D1+ includes N0. 110 and D2 includes Nos. 19,20,110 and 111.

For distal gastrectomy, the lymph nodes stations to be dissected in D1 lymphadenectomy are stations No.1, 3, 4sb, 4d, 5, 6 and 7; D1+ includes D1 stations plus stations No.8a, and 9, and D2 includes D1 stations plus stations No.8a, 9, 11p, and 12a.

LYMPH NODE DISSECTION FOR EARLY GASTRIC CANCER

The extent of lymphadenectomy in early gastric cancer (EGC) is strongly dependent from lymph nodal spread of early forms. It is well known that the probability of lymph node metastasis in EGC is much lower than in advanced forms. However, the risk ranges notably according to pathological characteristics of EGC. Invasion of submucosa, tumor grading, size, macroscopic appearance, and lympho-vascular invasion have been identified as strong risk factors for lymph node metastases in EGC[5]. As a consequence, these factors are taken into account for establishing the indications to endoscopic resection procedures (endoscopic mucosal resection, EMR, or endoscopic submucosal dissection, ESD) in the JGCA guidelines[4-6]. According to these predictive factors, subgroups of patients with virtual no risk of lymph node metastases have been identified. The resection is judged as curative when all of the following conditions are fulfilled: en-bloc resection, tumor size not greater than 2 cm, histology of intestinal-differentiated-type, pT1a, negative horizontal (lateral) margin, negative vertical margin, and no lymphovascular invasion. The JGCA "expanded" criteria tend to include larger tumor size, ulcerated or submucosal invading forms, and selected undifferentiated tumors in the indications to endoscopic treatment[7,8]. However, expanded criteria are not universally accepted and need validation in series outside East Asia[9].

In early forms not suitable for endoscopic treatment, the JGCA guidelines advice a D1 or D1 plus lymphadenectomy in cases with clinically negative nodes[4]. The D1 lymphadenectomy involves the removal of perigastric lymph nodes and station number 7, whereas in the D1 plus the lymph node stations 8a and 9 for subtotal gastrectomy, with the addition of station 11p for total gastrectomy, should be dissected. When lymph nodes are clinically positive, JGCA treatment guidelines advice a D2 dissection, which involves the removal of stations 12a and 11p in subtotal gastrectomy, and stations 12a, 11d and 10 in total gastrectomy[4].

In South Korea the treatment approach to early forms is similar[10]. In a recent study from Seoul National University Hospital (SNUH) the appropriate extent of lymph node (LN) dissection in lower third was evaluated analysing LN metastasis patterns from a prospective topographic database, using the Maruyama Index of unresected disease[11]. The evaluated risk of lymph node metastasis in stations 8-12 led the Authors to conclude that the D1 dissection plus stations 7 and 8a for mucosal cancer, and an expanded dissection to the D2 level for submucosal cancer should be considered to ensure complete removal of metastatic LNs.

In the West, the clinical setting is rather different from East Asia. In a large series of resected EGC from the Italian Research Group for Gastric Cancer (GIRCG) database, submucosal invasion, Lauren diffuse/mixed type, Kodama Pen A type and tumor size were found to be associated with an increased risk of lymph node metastases[12]. The risk of positive nodes is particularly high in diffuse-mixed type, an aggressive form of gastric cancer with special propensity to lymph node metastasis and peritoneal dissemination in advanced forms[13]. In the West, the decreasing incidence of gastric cancer is mainly due to the decreasing number of intestinal type tumors of the distal third; as such, proximal tumors and diffuse-mixed type show a relative increase, and surgeons will more frequently face with this aggressive form of gastric cancer[14,15]. Furthermore, endoscopic resections, which are treatment but also staging procedures, are much less adopted in the West, even if their implementation in clinical practice is increasing, above all in specialized centers[16]; as a consequence the diagnosis of EGC is clinically-based in most cases. Despite the recent advancement of staging procedures (CT scan, endoscopic US), the risk of a clinical understaging is still considerable, and this may be associated with a potentially fatal undertreatment, as the probability of advanced nodal status in non-early forms of gastric cancer in Western patients is notable[15]. For these reasons, the GIRCG guidelines advice a D2 lymphadenectomy in clinically early forms not suitable for endoscopic treatment[17]. Special attention should be given to the removal of infra-pyloric nodes (number 6), which are the most commonly involved in EGC of the distal stomach, above all in the diffuse-mixed type, and to station 1 (in subtotal gastrectomy) as well as to lymph node stations from 7 to 12 (station 10 is optional). The D2 dissection is associated with a limited risk of complications and postoperative mortality in the West, above all when performed in specialized centers and when avoiding unnecessary splenectomy or spleno-pancreatectomy[14,18]. Only in selected cases (high-risk patients, early forms with favourable pathological characteristics) more limited procedures

are adviced by the GIRCG group (D1 plus).

In any case, long term results reported in previous studies should be considered to optimize treatment approach. Surgical treatment with adequate lymphadenectomy could offer a high probability of cure even in Western patients. Survival rates in early stages reported from specialized Western centers are very similar to those obtained in Eastern series[19,20]. Selected forms can be treated by endoscopic approach, in accordance with the JGCA criteria, with acceptable results even in the West[16,21]. However, it should be emphasized that lymph node status is the strongest prognostic factor for EGC. Whereas 5-year and 10-year cancer-related survival of 98% and 95% can be achieved in pT1N0 cases treated with appropriate lymphadenectomy, these rates fall to 70%-80% in pT1N1/N2, and less than 30% when more than 6 lymph node are involved[12,20]. In T1N3a cases, the risk of recurrence could exceed 50%, reaching 80% in pT1N3b[22]. In Western patients, EGC with advanced nodal status should be considered very aggressive forms, requiring appropriate surgical and adjuvant treatments.

Early forms could also be treated by minimally-invasive (laparoscopic or robotic) approach, which demonstrated non-inferior oncological results than open surgery in recent studies[23,24]. However, it should be emphasized that oncological criteria regarding resection margin and lymph node dissection need to be carefully followed in minimally-invasive procedures.

D2 LYMPH NODE DISSECTION FOR ADVANCED GASTRIC CANCER

Gastric cancer is one of the leading causes of death for cancer worldwide[25,26]. In the latest decades in Eastern countries national screening programs have brought to earlier and widespread diagnosis while in Western countries diagnosis is often late, due to the lack of surveillance strategies[27]. In all the cases surgery is indeed the standard of care for all resectable tumours: radical gastrectomy with regional lymphadenectomy is considered the adequate treatment[28].

Gastric cancer has a high tendency to lymph nodes involvement and local spread: the deeper is the extension of the tumour the more they are invaded[29]. Nodal spreading gradually takes place radiating from the primary site[30,31] and nodal involvement is one of the most important prognostic factors. It is therefore clear the reason why surgeons have always given so much importance to lymphadenectomy and its extension

In fact, lymph node dissection has been debated for several years by surgeons: as a result, two different schools have developed[32,33]. In Eastern countries D2 lymphadenectomy has been considered the standard procedure since the 60's[34,35], in particular in Japan[1,36,37], where the high incidence of this tumour has always raised great interest. In Asian countries extended lymphadenectomy seems to give superior results in terms of survival and recurrence[38-42]: this could be explained by the Asian larger surgical experience with this kind of dissection[18,38,43-46] and by the younger age of Asian patients, who therefore have fewer comorbidities[38,47], and less abdominal fat with a consequent easier feasibility of the procedure[46]. A criticism that Western surgeons have advocated is that Japanese- and Asian in general-results were often provided by retrospective surveys and non-randomized studies[38,45,48].

On the contrary in Western countries D2 lymphadenectomy was not considered a standard procedure in the clinical practice[27,35,43]: the lower incidence of this tumour and the consequent less confidence of western surgeons in this procedure is surely one of the reasons. D2 is a complicated and challenging surgical technique and a proper training is mandatory. In addition, according to former studies [mainly Western randomized clinical trials (RCTs)[38,45,46,49] and subsequent reviews[50-54]] D2 seemed associated with higher rate of surgical complications and higher peri-operative mortality, without a real survival benefit. Driven by these results, Western surgeons have always preferred the limited dissection.

Recent data have undermined this historical preference and started to change Western point of view on D2 lymphadenectomy. In fact it has been demonstrated[28,45-48,55-58] that the higher rate of mortality and surgical complications with D2 procedure were mostly related to distal pancreatectomy and/or splenectomy, which previously were included in the standard D2 lymphadenectomy and considered necessary for an adequate nodal dissection. Older studies[18,36,44,47-52] included in the D2 group all patients treated with distal pancreatectomy and splenectomy: these patients had a higher mortality rate and a higher incidence of surgical complications (such as fistulas, re-intervention, anastomotic leakage *etc.*) which influenced their outcome. On the contrary in more recent studies[18,28,43,44,53] subsites of patients that underwent splenopancreatectomy and patients with spleen and/or pancreas preservation are analysed separately.

Furthermore it has been shown that even in Western countries, after a proper training, surgeons can safely perform a D2 gastrectomy when spleen and pancreas are preserved, leading to lower morbidity and mortality rates and to a safer lymph node dissection[18,44,58].

Last but not least the 15 year-follow up of the famous Dutch study[28] has demonstrated that loco-regional recurrence rate is significantly lower in patients treated with D2 lymphadenectomy *vs* patients who underwent D1 dissection, showing a survival benefit with the enlarged dissection.

Here after some of the most significant studies, RCTs, reviews and meta-analysis -over D1 *vs* D2 are

reported.

Dent *et al*[59] in 1988 described the first RCT recruiting 43 patients, 22 with D1 and 21 with D2 dissection: the D2 group showed a higher rate of perioperative complications without any significant benefit in survival after a follow up of three years.

In the 90's two multicentre European RCTs, the Dutch and the MRC trials, almost simultaneously, published their results comparing short and long-term outcomes after D1 and D2 LN dissection. In the Dutch trial[45], which randomised 711 patients (380 to D1 and 331 to D2), the D2 group showed a higher mortality rate (10% *vs* 4%, $P = 0.004$), a higher frequency of postoperative complications (43% *vs* 25%, $P < 0.001$) and a longer hospital stay (median 25 d *vs* 18 d, $P < 0.001$). In 1999 the same authors[46] reported the 5-year survival results: survival rates were similar in the two groups (45% in D1 *vs* 47% in D2). The risk of relapse after 5 years was 43% for the D1 group and 37% for the D2 group; the difference suggested only a trend of survival benefit for the D2 group ($P = 0.22$). In addition, patients who needed resection of the spleen or of the distal pancreas had a lower survival rate compared to those who did not require it; splenectomy was found to be an independent risk factor for surgical complications[60] and was associated with decreased survival in both D1 and D2 procedures. The authors concluded that splenectomy should not be a routine part of the standard gastrectomy.

In 2004 the Dutch Gastric Cancer Group published the long-term outcome of their trial[48] after 11 years follow-up: no overall survival benefit was demonstrated with D2 lymphadenectomy (30% with D1 *vs* 35% with D2, $P = 0.53$) and only in subgroup analysis patients with N2 disease showed higher survival rate after D2 than after D1procedure. The authors concluded that no overall survival benefit had been demonstrated with an extended dissection as the associated higher postoperative mortality may had offset D2 long-term benefit in survival; for that reason D2 dissection could have been of benefit only if mortality and morbidity could have been avoided.

In 2010 the results of 15-year follow-up of the same trial[28] were published. D2 lymphadenectomy was finally associated with lower loco-regional recurrence and gastric-cancer-related death rates, as compared to those of D1 ($P = 0.01$). Significantly lower overall survival was noticed in patients who underwent splenectomy and pancreatectomy in both D1 and D2 groups. Subgroup analysis of patients who did not undergo pancreatectomy and splenectomy showed significantly higher overall 15-year survival rate in the D2 group (35% *vs* 22%). The authors concluded that, since other studies[61,62] had recently demonstrated that even in Europe trained surgeons could safely perform D2 lymphadenectomy with spleen and pancreas preservation and that D2 showed more favourable recurrence pattern and cancer-related survival, D2 seemed to be the recommended treatment for patients with resectable gastric cancer (Table 3).

In the British study[38], whose short term survival results were published in 1996, 400 patients, 200 with D1 and 200 with D2, were recruited. The D2 group had greater postoperative mortality (13% *vs* 6.5%, $P = 0.04$), higher overall postoperative morbidity (46% *vs* 28%, $P < 0.001$) and longer hospitalization. Also Cuschieri *et al*[49] investigated the adverse effects of distal pancreatico-splenectomy, reporting that the disadvantages of D2 gastrectomy (*i.e.,* higher mortality and morbidity) might be the result of the additional pancreatectomies and splenectomies performed. The same authors in 1999 published the 5-year survival results of their trial[49] without showing any significant difference in the overall survival (35% in D1 and 33% in D2). In multivariate analysis clinical stages Ⅱ and Ⅲ, male sex, old age and especially resection of spleen and pancreas were found to have a significant influence on survival. The authors concluded that D2 gastrectomy did not offer any advantage in terms of survival over D1 gastrectomy and that pancreatico-splenectomy should not be considered a part of D2 dissection unless a direct involvement of the disease into the pancreas was suspected (Table 3).

In 1998 the Italian Gastric Cancer Study Group published the results of a prospective multicentre phase 2 study on feasibility of D2 gastrectomy with spleen and pancreas preservation[61-63]: pancreatico-splenectomy was not performed unless a direct involvement of the pancreas by the tumour was suspected. The authors showed that D2 gastrectomy with spleen and pancreas preservation could be done even in Western countries, in specialized centres, with a strict quality control and a after a period of adequate training. Mortality and morbidity rates were comparable to those of standard resection and even better, reaching figures similar to the Japanese ones. After these first cheering results, a randomised controlled trial was set up in 1998[58], in order to compare the short- and long-term outcome of D1 and D2 nodal dissection. A total of 267 patients with gastric cancer were randomly assigned to either a D1 (133) or a D2 (134) procedure with preservation of pancreas and spleen, in five specialized centres over a period of 6 years. In 2010 the Authors reported the short-term results. In the intention-to-treat analysis, the overall morbidity rate after D2 and D1 dissections were 17.9% and 12.0% respectively ($P = 0.178$). The postoperative in-hospital mortality rate was 3.0% in the D1 group and 2.2% after D2 gastrectomy ($P = 0.722$). The Authors concluded that in specialized centres the rate of complications following D2 dissection was much lower than in published randomized Western trials and therefore D2 dissection, in an appropriate setting, could be considered as a safe option for the radical management of gastric cancer in Western patients. In 2014 the Italian Gastric cancer Study Group published the long-term results of this RCT[18]. The five-year

Table 3 Results of randomised controlled trials on D1 *vs* D2 gastrectomy

RCT	Nr. pts		Morbidity (%)		Mortality (%)		Survival (%)	
	D1	D2	D1	D2	D1	D2	D1 (OS)	D2 (OS)
Bonenkamp *et al*[45,46]	380	331	25	43 $P < 0.001$	4	10 $P = 0.04$	45 (5 yr) 30 (11 yr) 21 (15 yr)	47 (5 yr) $P = 0.99$ 35 (11 yr) $P = 0.53$ 35 (15 yr) $P = 0.03$
Cuschieri *et al*[38,49]	200	200	28	46 $P < 0.001$	6.5	13 $P = 0.04$	35 (5 yr)	33 (5 yr) $P = 0.43$
Wu *et al*[55,56]	110	111	17.1	7.3 $P = 0.012$	0	0	59.5 (5 yr)	53.3 (5 yr) $P = 0.041$
Degiuli *et al*[18, 58]	133	134	12	17.9 $P = 0.178$	3	2.2 $P = 0.722$	66.5 (5 yr) 38 (DSS 5 yr T2-T4 N+)	64.2 (5 yr) $P = 0.695$ 59.0 (DSS 5 yr T2-4 N+) $P = 0.055$

RCT: Randomised controlled trial; OS: Overall survival; DSS: Disease specific survival; N+: Node positive patients.

overall survival (OS) and disease-specific survival (DSS) rates were respectively 66.5% and 71% for D1 and 64.2% and 72.6% for D2, with no significant difference between the two groups (OS $P = 0.695$, DSS $P = 0.916$). Subgroup analysis showed a trend towards benefit of D2 dissection in patients with locally advanced gastric cancer (DSS 55% for D1 *vs* 69% for D2 with $P = 0.143$) and in patients with positive lymph nodes (OS rate 35% for D1 *vs* 51% for D2 and DSS rate 38% for D1 *vs* 59% for D2). This survival benefit was even greater and close to reaching a statistical significance in the subgroup of patients with both these two variables (T2-T4, N positive): 5-year OS rate was 35 % for D1 and 51% for D2, with $P = 0.078$, while 5-year DSS was 38% for D1 and 59% for D2 ($P = 0.055$). Therefore the authors concluded that D2 might be a better choice in patients with advanced disease and lymph nodes metastasis (Table 3).

Wu *et al*[55] in 2004 published the first results of a trial comparing 110 patients undergoing D1 dissection and 111 undergoing D3 resection and their respective morbidity and mortality rates. The postoperative hospital stay was longer for D3 patients [mean (SD) 19.6 (13.9) (range 10-98) d *vs* 15.0 (4.0) (range 10-30) d, $P = 0.001$]. Morbidity rate was higher in the D3 group (17.1% *vs* 7.3%, $P = 0.012$), mainly due to a high incidence of abdominal abscess after D3 resection (8.1% *vs* 0%, $P = 0.003$). Patients with hemipancreaticosplenectomy had a higher morbidity rate (35.7% *vs* 10.6%, $P = 0.017$). In both group there was no operative mortality. The study confirmed the higher risk of complications after that extensive dissections and suggested that extensive lymph node dissection should be done by surgeons thoroughly experienced in the technique. In 2006 the same authors[56] published the 5-year survival results: overall 5-year survival was higher for D3 patients (59.5% *vs* 53.3%, $P = 0.041$). The authors concluded that even if D3 lymphadenectomy was associated with a higher morbidity, due to its surgical complexity, it had a significant long-term survival benefit over D1 dissection (Table 3).

Seevaratnam *et al*[57] in 2012 analysed 5 randomized trials involving 1642 patients (845 D1 and 797 D2) enrolled from 1982 to 2005; the authors highlighted the differences among earlier (considering procedures with spleen and pancreas removal) and more recent trials (with spleen and pancreas preservation). As concerns the short-term outcomes, overall hospital mortality was significantly higher for D2 patients (7.5% *vs* 3.8% with RR of 2.02, $P = 0.002$); subsite analysis showed that hospital mortality was still significantly higher for D2 patients in early trials (10.5% *vs* 4.6%, $P = 0.0003$), while it was similar in recent trials (1.5% for D1 *vs* 1.2% for D2, $P = 0.70$).

The overall 5-year survival rate showed similar results for D1 and D2 patients (43.5% and 44.9%, $P = 0.58$). In subgroup analysis no significant difference was found between T1/T2 patients (55.4% for D1 and 52.3% for D2, $P = 0.46$) while a trend of survival benefit in favour of D2 was identified for more advanced tumours (13.5% for D1 *vs* 19.5% for D2 in patients with T3/T4). In addition, the subgroup of patients with spleen and pancreas preservation showed a trend towards better survival rate with D2 compared to D1 (54.9% *vs* 43.0%). The authors concluded that while older trials favoured D1, the more recent trials did not show any significant differences in mortality between the two procedures, demonstrating that D2 gastrectomy could be performed safely, mostly due to the preservation of spleen and pancreas.

In 2014 Jiang *et al*[35] analysed 8 RCTs published between 1988 and 2010, with a total of 2044 patients (1042 D1 and 1002 D2). D2 gastrectomy resulted associated with significantly greater morbidity in terms of anastomotic leakage, pancreatic leakage,

reoperation rates, wound infection and pulmonary complications. The overall 5-year survival rate did not show any significant difference between the two groups. Overall postoperative mortality was significantly lower in the D1 group (RR = 0.58, 95%CI: 0.47-0.71, $P < 0.001$) but in subgroup analysis no difference was found between patients with pancreas and spleen preservation in D1 and D2 groups (RR = 1.35, 95%CI: 0.45-4.05 for pancreas resection; RR = 0.85, 95%CI: 0.47-1.54 for spleen resection), showing that the higher mortality associated with D2 in older trials was highly influenced by spleen and/or pancreas resection. The authors reported also a trend towards a lower risk of gastric cancer-related death in D2 patients with spleen and pancreas preservation.

Anyway, in the latest years the consensus on D2 lymphadenectomy has increased worldwide[28,57,64-78], since a trend of improved survival among D2 patients was recorded and published mainly due to spleen and pancreas preservation and to the increase of skillness and experience on D2 technique in high volume reference hospital.

Evidence based medicine (EBM) and practical surgical experience seem now to move towards an international agreement: nowadays D2 procedure is recommended as the standard procedure by the Japanese[3], Korean[10], German[79], British[80], Italian[81], European Society for Medical Oncology (ESMO)[82] and the joint ESMO- ESSO (European Society of Surgical Oncology)- ESTRO (European Society of Radiotherapy and Oncology) guidelines[83]; in addition, more recently NCCN recommends D1+ or modified D2[84] also in the United States.

D2+ FOR ADVANCED GASTRIC CANCER

Whether the extension of lymphadenectomy beyond the standard D2 dissection could add any benefit in the treatment of advanced gastric cancer, is a controversial issue.

The routine lymphadenectomy of para-aortic nodes (PAN), which has been practiced extensively by Japanese surgeons and in specialized Western centres in the past decades, is currently no more indicated after the publication of the Japan Clinical Oncology Group (JCOG) 9501 trial[85]. Indeed, the results of the Japanese trial showed no survival benefit after D2 plus PAN dissection compared to D2 lymphadenectomy alone in advanced gastric cancer without clinical suspicion of PAN metastases[85].

Nevertheless, in the JCOG9501 trial, a rather high 5-year survival (18.2%) was reported in patients with positive PAN after a prophylactic PAN dissection. Also, similarly, in some Eastern and Western series, including cases with clinical involvement of PAN, long-term survivals were reported, after PAN dissection, in patients with pathologically positive PAN[86], especially in the absence of incurable factors[87].

Therefore, some authors suggested the need of further evaluations before definitively rule out the PAN dissection by therapeutic options for treatment of advanced gastric cancer[88,89].

Interestingly, in a recent phase Ⅱ trial from the Stomach Cancer Study Group of the Japan Clinical Oncology Group[90], patients with locally advanced gastric cancer with extensive regional (N2) nodes and/or PAN metastases were treated with neo-adjuvant chemotherapy (S-1 plus cisplatin) followed by extended surgery with PAN dissection. The 3- and 5-year overall survival rates were of 59 and 53 per cent, respectively.

Based on these results, Japanese surgeons are now suggesting that extended D2 plus PAN dissection after neo-adjuvant chemotherapy could be considered as a promising treatment for patients with clinically detected PAN involvement or with extensive N2 nodal metastases[91].

Anyway, we need further evaluations regarding the benefit of dissecting nodal stations other than PAN whose removal is currently no more indicated, and the identification of subgroups of advanced gastric patients who may definitely benefit from D2+ dissection after neo-adjuvant chemotherapy.

Indeed, according to the last version of Japanese guidelines[4], the standard D2 dissection does not include the removal of lymph nodes along the superior mesenteric vein (No. 14v). Of note, No. 14v station was comprised in the N2 compartment for lower third gastric tumours in the second edition of Japanese Classification[3] and was part of the D2 dissection for distal tumours in the JCOG9501 trial.

But, even in the lack of specific evidences a D2+ No 14v nodes is, currently, considered only in case of tumours with apparent metastases to infra-pyloric nodes. Recently, a Korean study[92] showed that 14v lymph node dissection was an independent prognostic factor in patients with clinical stage Ⅲ/Ⅳ gastric cancer of the middle and lower third, therefore future investigations on this topic are necessary.

Also, the dissection of posterior nodal stations (No. 8p, 12p, 13), which were routinely removed during a super-extended (D3) lymphadenectomy and, in case of retro-pancreatic (No. 13) nodes, were comprised in the standard D2 dissection for distal tumours in the JCOG trial, is at present, no more indicated.

In a recent observational study of our GIRCG group, super-extended (D3) lymphadenectomy which included the systematic removal of posterior stations (8p, 12p, 13, 16a2 and 16b1), was associated with a significant lower incidence of loco-regional relapses when compared to the standard D2 dissection in advanced gastric cancer with mixed-diffuse histology[93]. These results suggest a possible therapeutic role of the dissection of posterior stations other than PAN (8p, 12p. 13). Moreover, we observed that subgroups of tumours with a greater lymphotropism are better controlled by a super-extended lymphadenectomy. In our study none of the

patients had received preoperative chemotherapy.

Based on these findings, dedicated randomized trials are needed to provide specific evidences on the optimal extension and the indications of D2+ lymphadenectomy after neo-adjuvant chemotherapy in advanced gastric cancer.

LAPAROSCOPIC LYMPH NODE DISSECTION

In recent years, through the development of minimally invasive techniques and improvement of the devices for laparoscopic surgery, several surgeons have started applying laparoscopic assisted gastrectomy (LAG) for gastric cancer.

Although several potential benefits of LAG compared to conventional open procedure - such as less post-operative pain, cosmetics, less blood loss, faster recovery, and shorter hospital stay - minimal invasive surgery for gastric cancer has not yet achieved a solid evidence-based validation; up to 2010, the Japanese Gastric Cancer Treatment Guidelines did not recommend LAG in a curative cancer resection setting, but indicated laparoscopic gastrectomy just as an investigational procedure eligible for clinical trials[4].

To date, two prospective trials (KLASS 01, JCOG 0703)[94,95] and several retrospective studies argue the safety and oncological feasibility of laparoscopic surgery for the treatment of EGC. The results of these studies demonstrate both the reliability of laparoscopic lymphadenectomy in terms of oncological radicality as well as the absence of differences in the complication rate and short-term results between laparoscopic and open surgery. Therefore, along with the demonstration that the number of harvested lymph nodes by LAG to date has increased up to reach that observed during open gastrectomy, laparoscopic gastric surgery has now to be considered at least as "feasible".

Most recent reports investigating the short-term results of laparoscopic gastric surgery refer to EGC; these data obviously can not be directly transferred to what is expected for advanced gastric cancer (AGC) and it is extremely important to differentiate the results related to early tumors from those related to advanced tumors.

EGC

As concerns early gastric cancer a phase Ⅲ multicenter prospective randomized trial (KLASS Trial)[94] has concluded that there is no significance difference in morbidity and mortality between laparoscopy assisted distal gastrectomy and open distal gastrectomy. Possible disadvantages are the longer operative time and the steep learning curve for laparoscopic surgery.

The same group to provide background data for KLASS trial, present one of the largest case-matched series, comprising about 3000 patients with surgically resectable gastric cancer (approximately 1500 laparoscopic and 1500 open gastrectomies over a 7-year period), comparing the long-term results of laparoscopic with open approach[96].

In this study, at a median follow-up of 70.8 mo the overall survival, disease-specific survival, and recurrence-free survival were not statistically different except for patients with stage IA disease treated with laparoscopic surgery, who showed an increased overall survival rate (laparoscopic group; 95.3%, open group: 90.3%; $P < 0.001$) probably attributable to selection bias.

It is well known that the number of lymph nodes removed during gastrectomy is to be correlated with the prognosis of gastric cancer. In past years the number of lymph nodes collected during laparoscopic lymphadenectomy was lower compared to open lymphadenectomy. In recent years, through the improvement of laparoscopic surgical techniques and skills of surgeons, the number of dissected lymph nodes has gradually increased, reaching that observed after open gastrectomy.

Ohtani *et al*[97] in a meta-analysis conducted on four randomized control studies[97-100] comparing laparoscopic distal gastrectomy LADG with open distal gastrectomy (ODG) for EGC, has shown that the number of harvested lymph nodes was higher in the ODG group than in the LADG group, although this difference was not statistical significant except in one of the four studies. A recent meta-analysis of eight case-control studies has revealed that there is no evident difference in the number of lymph nodes dissected, between LADG and ODG[101]. The mean operative time for LADG is significantly higher than ODG. Kodera *et al*[102] has shown that the mean operating time in the LADG group ranged from 196 to 348 min, that appears to be certainly longer than the time needed to accomplish an ODG in all studies. This finding could be due to the reduction of the field of view, lack of tactile sensation, and the steep learning curve needed for LADG. In the near future, with the advancements in surgical techniques and laparoscopic devices, the time required for laparoscopic-assisted gastrectomy is probably going to decrease.

Laparoscopic total gastrectomy

Differently from LADG, techniques for laparoscopic total gastrectomy (LTG) has not yet been standardized, therefore it remains a challenging procedure. Some technical difficulties involved in D2 lymphadenectomy, such as a safe dissection of the No. 10 lymph nodes, and a standardized laparoscopic anastomosis technique, may constitute an obstacle in applying laparoscopic surgery for proximal cancer.

A recent metanalysis[103] including eight non-RCTs was published. There were compared the short term results of 314 LTG and 384 open total gastrectomy (OTG) in patients with gastric cancer. In hospital mortality rates were comparable between two groups

(LTG 0.9% - OTG 1.8%).

Patients in LTG group, despite a longer operative time, seem to have less intraoperative blood loss, less postoperative complications, and shorter hospital stay compared with OTG.

The results of this metanalysis showed that LTG has better short-term outcomes compared with OTG. Despite these encouraging results data on LTG are still limited. In South Korea, a multicenter phase Ⅱ trial (KLASS-03) trying to assess the feasibility of LTG for stage I gastric cancer is currently ongoing.

AGC

Another issue requiring further clarification is the application of laparoscopic surgery in AGC. Thus, if laparoscopy gastrectomy (LADG) has been increasingly used for EGC and T1-T2 tumors, still it has been less investigated as regards AGC; it is currently matter for debate if LAG with D2 lymphadenectomy should represent an appropriate treatment for an AGC as well[104,105]. Challenging technical issues could be represented by large-size tumors or tumors that require multiorgan resection.

To date, short-term results and complication rate of laparoscopic gastrectomy with D2 lymph nodes dissection for advanced gastric cancer are still controversial. Many authors have reported no difference between laparoscopic and open procedures in terms of number of harvested lymph nodes[106-108]. Shuang *et al*[109] has reported a median number of 35 lymph nodes dissected in the laparoscopic group *vs* 38 in the open group, which is comparable to the number reported by other authors who performed laparoscopic surgery for AGC[107,110,111]. Analyzing the data in literature the postoperative morbidity rates of LAG for advanced gastric cancer ranges from 7.7% to 31.5%[94,112,113]. Cai *et al*[114] has reported that the overall morbidity rates were 12.24% in the LAG and 19.15% in the OG groups, with no significant difference. However, respiratory complications were more frequent in the OG group.

Learning Curve

Another important issue for laparoscopic lymphadenectomy is the learning curve. In a recent korean series, in order to improve lymphadenectomy skills and decrease complications at least 42 gastrectomies were required[96].

Therefore, an extensive case-load is required to individual surgeons in order to perform a safe laparoscopy assisted gastrectomy; a precise standardization of laparoscopic procedures together with a considerable number of cases are needed for an efficient educational system. Only the high-volume certified centers can provide the number required to the clinical application and teaching of laparoscopic techniques for gastric cancer[115].

The achievement of reliability of laparoscopic lymphadenectomy in terms of oncological appropriateness and the absence of differences as regards the incidence of complications and short-term results between laparoscopic and open approach, have allowed the transferral of the many advantages of mini-invasiveness to the treatment of early gastric cancer. This has been made possible through the development of newly designed operative techniques and the introduction of better technological devices for laparoscopic surgery together with the undoubted improvement of surgical skills. Up to date laparoscopy assisted gastrectomy with D2 lymph node dissection for the treatment of advanced gastric cancer is a promising oncological procedure with adequate lymph node harvesting. The advantages of minimal invasion, including the reduced risks of surgical related trauma, the containment of blood loss, less postoperative pain and earlier recovery could lead to a reduction in complications for difficult patients such as those with advanced gastric cancer. Confirmation of the appropriateness and safety of laparoscopic assisted gastrectomy for patients with advanced gastric cancer are expected from the results of different prospective studies comparing the short- and long-term outcomes (KLASS 02, CLASS 01, JLSSG 0901), which are currently in progress.

ROBOT ASSISTED LYMPH NODE DISSECTION

Modern oncology offers a huge step forward in more effective treatment of a cancer using modern and advanced equipment to improve the quality of care[116-120]. The role of robotic gastric cancer surgery is increasing, but still no strong and clear evidence has been reported to support the superiority of this approach over others. Clearly it shows advantages in comparison with laparoscopic by the use of twisted instruments with 7 degrees of freedom and motion scaling, tremor filtering and 3D visualization images of high resolution. It is clear that laparoscopy led us with magnifying anatomical structures to perform more precise lymphadenectomy. Using laparoscopical approach surgeons had to face with limitation of movements, linear laparoscopic tools, tremor transfer of the surgeon's hand to the tip of the forceps, and 2D visualization without proper sense of depth. Robotic surgery seems to solve all of these disadvantages. The high resolution image with 3D visualization technology is especially useful in infrapyloric, suprapancreatic area and splenic hilum, where an adequate recognition of tiny anatomical structures during lymphadenectomy is of the highest importance. The endowrist instruments might be especially helpful during lymphadenectomy in suprapancreatic area where it seems to be more difficult in laparoscopic setting using linear instruments.

In retrospective studies in majority from eastern countries they compare laparoscopic and robotic approach sometimes also with open technique. Woo *et*

al[121] showed that robotic approach is associated with longer operative time. From the other hand less blood loss was observed during robotic surgery. Analyzing morbidity (11%) and mortality (0.4%) there were no difference between both techniques ($P > 0.05$). Also the numbers of dissected lymph nodes were similar. In paper by Kim *et al*[122] that compared overall complications, reoperation and mortality rates were similar in open, laparoscopic and robotic approach. The only difference was observed in anastomotic leakage which was more common in minimally invasive than in open approach ($P = 0.017$). It is probably because of usage staplers that were not used in minimally invasive techniques.

Currently we have few reviews and meta-analysis that analyzed problem of advantages in using robotic surgery during gastrectomy[123-127]. The results showed a lower amount of blood loss, but with longer time of operation. An explanations underline that the docking time might be responsible for prolonging the operation, and stable grasping and tissue retracting may help in better recognition of anatomical structures that lead to safer and less bloody procedure. The prolonged time of operation is also associated with more complicated lymphadenectomy especially with comparison to open technique. It is worth to note that no significant difference was observed according to the number of harvested lymph nodes. Also no difference was seen when analyzing overall complications rate and mortality.

Analyzing survival we have only 2 non randomized studies that compare robotic with open approach and one non-randomized study that compare laparoscopic and robotic one[128-130]. In publication by Caruso *et al*[130] no significant differences in overall survival rates was observed. Pernazza *et al*[128] proved that robotic surgery was associated with improved survival in comparison with open technique. This improvement was observed especially in advanced gastric cancer patients. In paper by Pugliese *et al*[129] 5-years survival was 85% for robotic and 75% for laparoscopic but without statistical significance.

Marano *et al*[127] analyzed technical benefits of robotic approach in gastric cancer surgery. They emphasized the improvement in performing lymphadenectomy in infrapyloric, suprapancreatic region, in splenic hilum and superior mesenteric vein. In paper by Son *et al*[131] where they compared spleen preserved robotic and laparoscopic D2 gastrectomy no difference between these two approaches was observed in terms of number of dissected lymph nodes, complications rate, and mortality rate. Interestingly they observed higher number of retrieved lymph nodes along splenic artery and splenic hilum in robotic approach. Higher number of retrieved lymph nodes was not associated with improvement in survival but of course led to improvement in staging of the disease. Seems that lower morbidity might be the most important benefit from robotic gastric cancer surgery. In paper by Suda *et al*[132] in comparison of laparoscopic with robotic approach the local complications rate (robotic *vs* lap 1.1% *vs* 9.8%, $P = 0.007$) and morbidity (2.3% *vs* 11.4%, $P = 0.009$) were statistically significantly lower as robotic technique was used. These authors underline the fact that in their series no pancreatic fistulas were reported. It is probably because of better anatomy visualization during lymphadenectomy and less traumatic access to the pancreatic parenchyma during robotic tissue preparation. In multicentric prospective study from South Korea the authors compared robotic with laparoscopic gastrectomy[133]. The complications rates were similar, without mortality in both arms. Robotic approach was associated with longer time of operation and higher costs. The authors conclude that perioperative surgical outcomes in robotic technique are not superior to laparoscopic one. Noshiro *et al*[134] analyzed using a monopolar scalpel in robotic lymph node dissection. They underlined a stable visualization of the operative field that can help in better understanding of the anatomy and proposed to use a term "robotically-enhanced surgical anatomy". The authors proved that robotic operation was associated with lower blood loss and lower rate of pancreatic fistula.

The most difficult part of widely usage a laparoscopic approach in gastric surgery is a complicated lymphadenectomy, and it is difficult to implement that into a routine practice[135]. It seems that usage of robotic may help in standardization of gastric cancer lymphadenectomy. The robotic approach may probably help in more precise and safer operation especially of some most critical lymph nodes stations like No. 6, 5, 1, 14v, and suprapancreatic area with stations 7, 8a and 9[136,137]. The greatest attention is directed to station nr 6 and suprapancreatic area because of its dissection is close to anterior surface of the pancreas. The anatomical differences in this area presented by Haruta *et al*[138] might be responsible for technical problems in this area. Any mistake in this area may lead to pancreatic parenchyma penetration followed by pancreatitis with local fistula and even a leakage if the duodenal stump[138]. Another difficult lymph node station dissection is number 10 in splenic hilum. Problems with bleeding in this area often lead to perform splenectomy. Robotic approach probably might help in better recognition of the anatomical planes and safer dissection even in mostly dangerous areas.

Another point of interest is a usage of robotic technique in obese patients especially that in western countries many patients show high body mass index (BMI) status. Theoretically obese patients may have a benefit form robotic approach because of technically demanding D2 lymphadenectomy especially around vessels when a fatty tissue might be a problem in adequate exposition of the surgical field. In paper by Park *et al*[139] patients were classified to obese and non-obese group according to visceral fat area (VFA).

Interestingly the complete number of total and N2 area lymph node number was higher in non-obese patients with VFA < 100 cm^2. There were no differences in obese patients. Statistically significant robotic approach was associated with lower rate of severe complications after total gastrectomy in non-obese patients. The problem of obesity was also analyzed by Lee *et al*[140]. They compared subtotal gastrectomy with D2 lymphadenecotmy in laparoscopic and robotic approach in patients of different BMI status. In different BMI groups no significant difference in the rate of dissection of more than 25 nodes was observed between two techniques, but it is worth not note that laparoscopic approach had a significantly lower rate of retrieving more than 25 nodes in high BMI patients (P = 0.006). In high BMI patients the complications rate was comparable.

Even as the role of extended lymphadenectomy in gastric cancer is still under debate no doubts this technique requires high level of experience. The full robotic interaortocaval nodal dissection was performed by the team Roviello *et al*[141] and proposed as a feasible technique in selected cases.

Another field of research and possible usage of robotic surgery in gastric cancer treatment is dissection of posterior lymph nodes during lymphadenectomy. In Siena University unpublished data the chances of metastases in stations 8p, 12p and 13 are 5.1%, and rise to 15.4% as we have a T3 tumor in distal part of the stomach- the latest data were presented during International Gastric Cancer Conference in Sao Paulo 2015. This kind of lymphadenectomy is demanding and technically difficult in laparoscopic approach and in selected patients where the chances of cancer spread to these stations is the highest seems to be justified. From minimally invasive approach usage of robotic technique seems to be the optimal solution in this tailored treatment of advanced gastric cancer in western countries.

CONCLUSION

EGC can be successfully treated by endoscopic mucosal resection or endoscopic submucosal dissection, in reference centers with high operator and hospital volumes, when restricted or extended Gotoda's criteria can be applied and D1+ surgery is offered only to patients not fitted for less invasive treatment.

Furthermore, two randomised controlled trials have been demonstrating the non inferiority of laparoscopic technique as compared to standard open surgery for the treatment of early cases. Moreover, the feasibility of adequate D1+ dissection has been recently demonstrated also for the robot assisted technique.

In case of AGC the debate on the extent of nodal dissection has been open for many decades. While D2 gastrectomy was performed as the standard procedure in eastern countries, mostly based on observational and retrospective studies, in the west three RCTs (MRC, Dutch and IGCSG trials) have been conducted to show a survival benefit of D2 over D1 with EBM. While the MRC trial failed to show a survival benefit after the D2 procedure, mostly due to the significant increase of postoperative morbidity and mortality, which was referred to splenopancreatectomy, the Dutch trial could report a significant decrease of recurrence after D2 procedure at 15 years from the conclusion of its accrual. Recently, also the long term survival analysis of the Italian RCT could demonstrate a benefit for patients with AGC and positive nodes treated with D2 gastrectomy without splenopancreatectomy.

As nowadays also in western countries D2 procedure can be done safely with pancreas preserving technique and without preventive splenectomy, it has been suggested in several national guidelines as the recommended procedure for patients with AGC.

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