

## **D2 lymph node dissection: on the way to implementation in European population of patients with gastric cancer**

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*"Modern gastric cancer surgery is largely lymphatic collector surgery. The surgeon is obliged to make full use of broad preventive lymph node dissection as an important independent predictor".*

*M.I. Davydov (2011) [1]*

Radical surgeries of malignant tumors traditionally comprise mandatory one-piece removal of regional lymph nodes (LNs). This approach was introduced over 100 years ago by an American surgeon W.S. Halse. Yet, up till now it has been used to determine the tactics of cancer surgery in basic sites, including tumors of the gastrointestinal tract. Despite its high clinical effectiveness and unconditional standardization in the Asian region, the extended volume of lymph node dissection (LD) (the so-called D2 lymph node dissection) in gastric cancer (GC) surgeries hasn't been widely practiced by surgeons in Europe and both Americas up to the recent years.

As far back as several decades ago the need for an extended volume of LD application in GC surgeries was highlighted by H. V. Bondar [2], A. A. Klymenkov, Yu.I. Patyutko [3] and M.Z. Syhal [4]. However, until recent years, European clinical recommendations for cancer treatment did not suggest D2 LD as a surgical standard of providing surgical care to the general public [5].

The relevance of this issue is also proved by the results of central randomized trials, which formed the basis for the establishment of national standards for GC combined treatment in Western countries. Thus, in the MAGIC trial, the results of which laid the basis of standard GC combined treatment in the European Union, D2 LD was performed only on 42.5% of patients [6]. The North American standard of GC combined treatment is based on INT 0116 trial [7], in which an extended volume of LD was performed only on 10% of patients. In a large-scale clinical trial of perioperative chemoradiotherapy effectiveness known as CRITICS trial taking place in Europe today, the planned volume of LD to be used is smaller than D2 [8]. Thus, the issue of regional LD volume standardization in GC surgical treatment in the European population of patients remains relevant.

The process of lymph efflux out of the stomach remains within a complex and multidirectional system [9]. In all cases lymph fluid from different sections of the stomach is drained into the paraaortal LN collector through the chosen system – one of four main lymph efflux ways: the left subdiaphragmatic way (goes through the LN in the circulation of the left lower diaphragmatic artery), the abdominal way (goes through the LN along the left gastric, splenic, common hepatic artery and celiac trunk), the upper mesenteric way (receives lymph from subpyloric LNs and runs along the upper mesenteric artery) and the retropancreatic way (associated with LNs of the hepatoduodenal ligament, upper mesenteric vessels and common hepatic artery). Both left subdiaphragmatic and abdominal ways drain lymph from the upper third part of the stomach, whereas lymph efflux from its body runs primarily through the abdominal way and lymph efflux from the distal divisions through the abdominal, upper and mesenteric retropancreatic ways [10].

Metastases occurring in regional LNs are diagnosed in 37-65% of patients with gastric corpus cancer, in 44-80% of patients with tumors in the proximal sections and in 50-59% of cases with tumors localized in the distal sections of the stomach [11, 12]. Lesions of regional LNs directly depend on the depth of primary tumor invasion: in cases with intra- and subepithelial tumors the regional lymphogenous metastases are diagnosed in 0-5,5% and 19-31% respectively [1, 11, 13], in case of muscle

membrane or subserous layer invasion the lesion levels of regional LNs increase up to 30-62%, of serous membrane - up to 74% and reach 90-91% in case of infiltration of adjacent organs [1, 11].

The first one-piece tissue dissection of regional lymphogenous metastasis areas in the course of GC surgery was carried out in 1962 by D. Jinnai [14]. Since then, the concept of extended radical LD has become an essential stage in the strategy of GC surgical treatment in Japan. The research in the field of lymph node topography and extended clinical efficiency has formed the basis of the first edition of “General Rules for the Gastric Cancer Study”, which was published in the early 60s of the last century under the auspices of the Japanese Research Society for Gastric Cancer [15]. The first English edition of these Rules was published in Europe only in 1995. Today, on the basis of research performed by the Japanese Gastric Cancer Association (JGCA) a second English edition on the classification of gastric cancer JGCA was brought to life [16] as well as Japanese gastric cancer treatment guidelines (JGCA) [17], according to which the following groups of stomach LNs are distinguished (Table 1, Figure 1).

Table 1. The lymphatic system of the stomach [16]

LN Groups	LN Topography
№1	Right paracardiac LNs
№2	Left paracardiac LNs
№3	LNs along the lesser curvature
№4sa	LNs along the short gastric vessels
№4sb	LNs along the left gastroepiploic vessels
№4d	LNs along the right gastroepiploic vessels
№5	Suprapyloric LNs
№6	Infrapyloric LNs
№7	LNs along the left gastric artery
№8a	LNs along the common hepatic artery(Anterosuperior group)
№9	LNs at the celiac trunk
№10	LNs at the splenic hilum
№11p	LNs along the proximal splenic artery
№11d	LNs along the distal splenic artery
№12a	LNs in the hepatoduodenal ligament (along the hepatic artery)

№12b	LN in the hepatoduodenal ligament (along the bile duct)
№12p	LN in the hepatoduodenal ligament (behind the portal vein)
№13	Retro-pancreaticoduodenal LNs
№14a	LNs along the superior mesenteric artery
№14v	LNs along the superior mesenteric vein
№15	LNs along the middle colic vessels
№16	Para-aortic LNs
№17	LNs on the anterior surface of the pancreatic head
№18	LNs along the inferior margin of the pancreas
№19	Infradiaphragmatic LNs
№20	LNs in the esophageal hiatus of the diaphragm

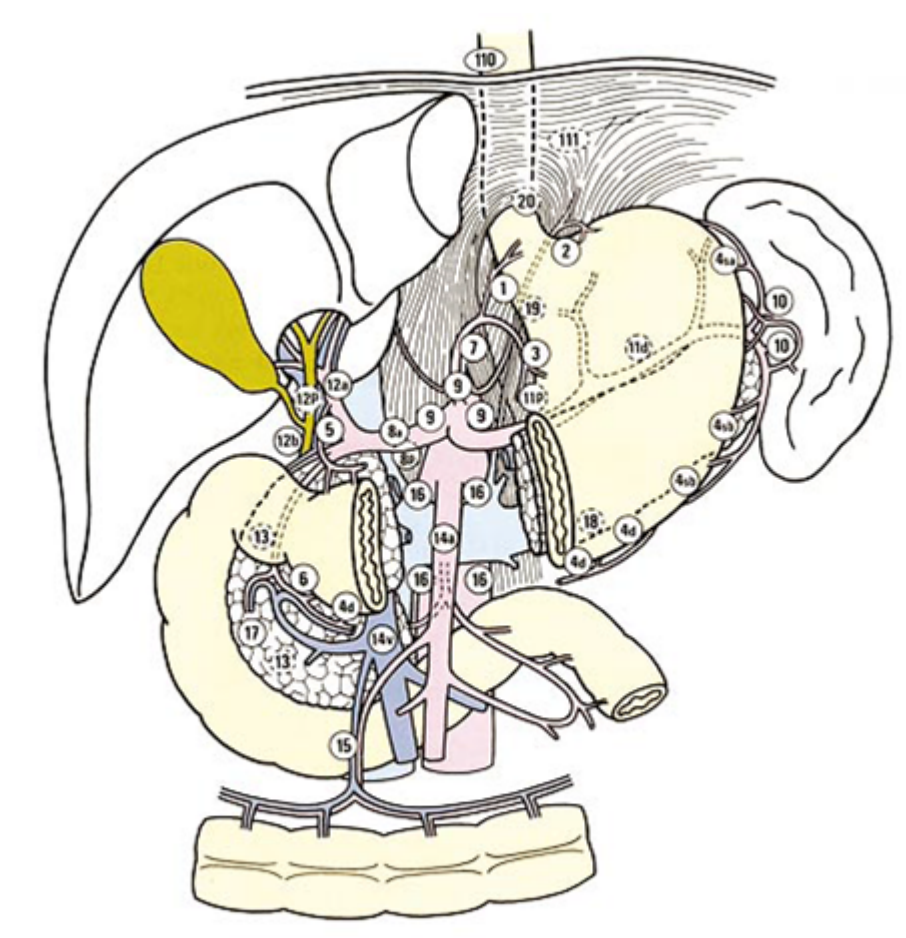


Fig. 1. Topography of stomach lymph node groups [16]

According to the classification of gastric cancer JGCA (1998) [16], the stomach lymphatic system consists of three LN stages. Each of them appears to be a temporary barrier that prevents tumor cells from getting into the lymph flow system.

Grouping stomach lymph collectors into stages will create the basis for determining the gradation of category «N» at staging and a theoretical basis for further LD volume justification. Thus, LN groups 1-6 affected by metastatic process are classified as N1, the lesion of LN groups 7-12 as N2, and the lesion of LN groups 12b, p and above as N3 (in the given classification it is equivalent to distant metastases). It should be noted that in the TNM classification introduced by the Union for International Cancer Control (UICC) [18] category «N» is determined not by the topography but by the number of affected regional LNs. According to Japanese gastric cancer treatment guidelines JGCA (2011) [17], lymph nodes from 1 to 12a groups are considered to be regional. LN groups - №2, 4sa, 10 and 11d are exceptions, which in distal stomach tumor cases are not considered regional and are referred to as lymphogenous metastases. Also, exception list includes LN groups - №5, 6, 12, which in proximal stomach tumor cases are considered as distant metastases [16 17].

In this respect, according to the classification of gastric cancer introduced by JGCA and Japanese gastric cancer treatment guidelines [16, 17], the option of surgical lymph node dissection is classified based on the last removed stage of regional LN depending on the tumor site in the stomach. Thus, during distal subtotal gastrectomy the lymph node dissection levels are as follows:

D0: LD in a volume less than D1

D1: №1, 3, 4sb, 4d, 5, 6, 7

D1 +: D1 plus №8a, 9

D2: D1 plus №8a, 9, 11p, 12a (Fig. 2).

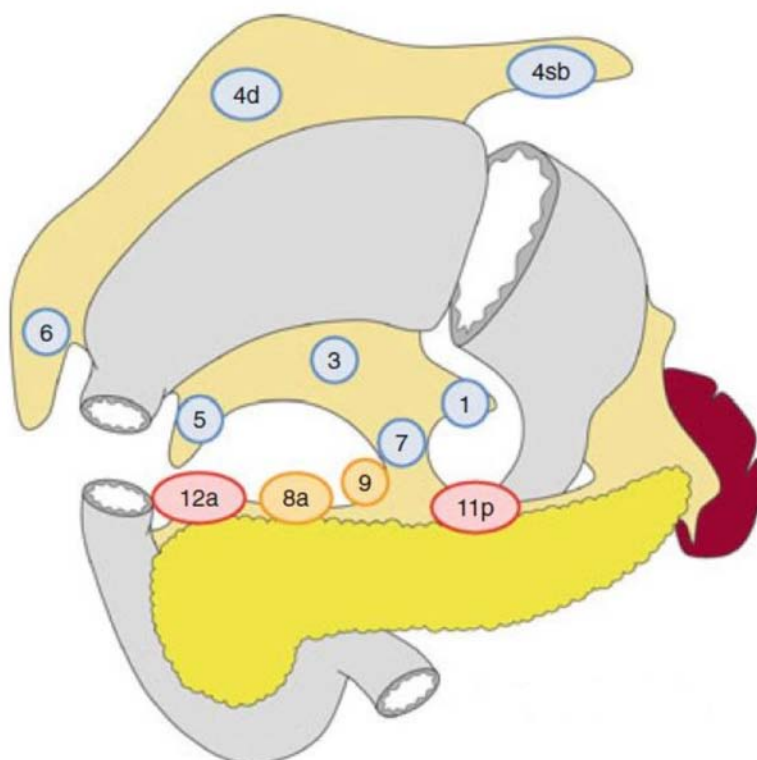


Fig. 2. Lymph node dissection levels in distal subtotal gastrectomy [17]

While performing gastrectomy, the lymph node dissection levels are as follows:

D0: LD in a volume less than D1

D1: №1-7

D1 +: D1 plus №8a, 9, 11p

D2: D1 plus №8a, 9, 10, 11p, 11d, 12a (Fig. 3).

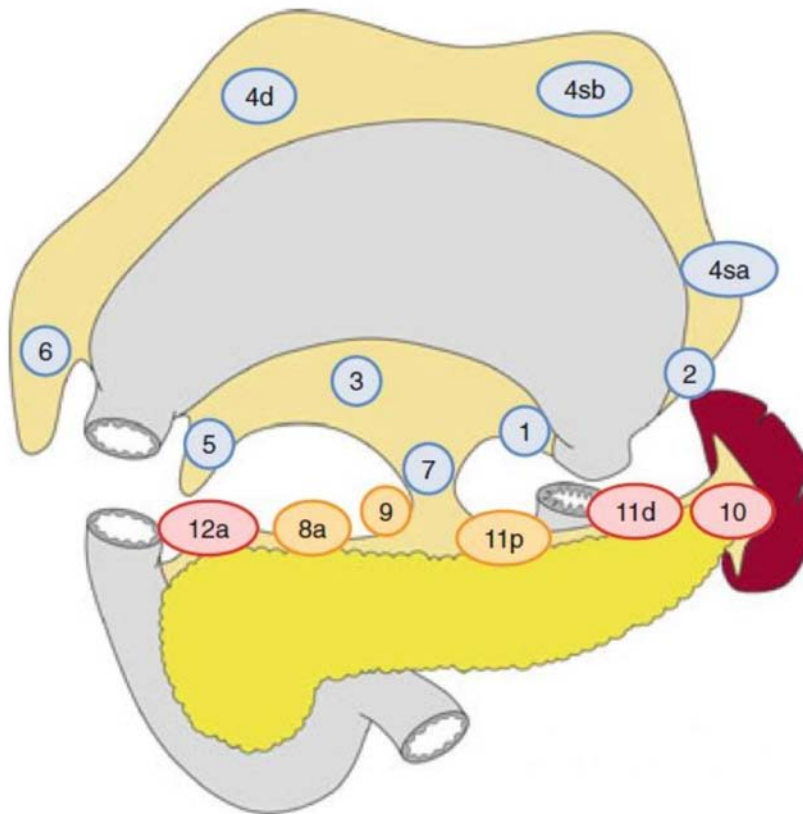


Fig. 3 Lymph node dissection levels in gastrectomy [17]

Levels of lymph node dissection while performing proximal subtotal gastrectomy:

D0: LD in a volume less than D1

D1: №1, 2, 3a, 4sa, 4sb, 7

D1 +: D1 plus №8a, 9, 11p (Fig. 4).

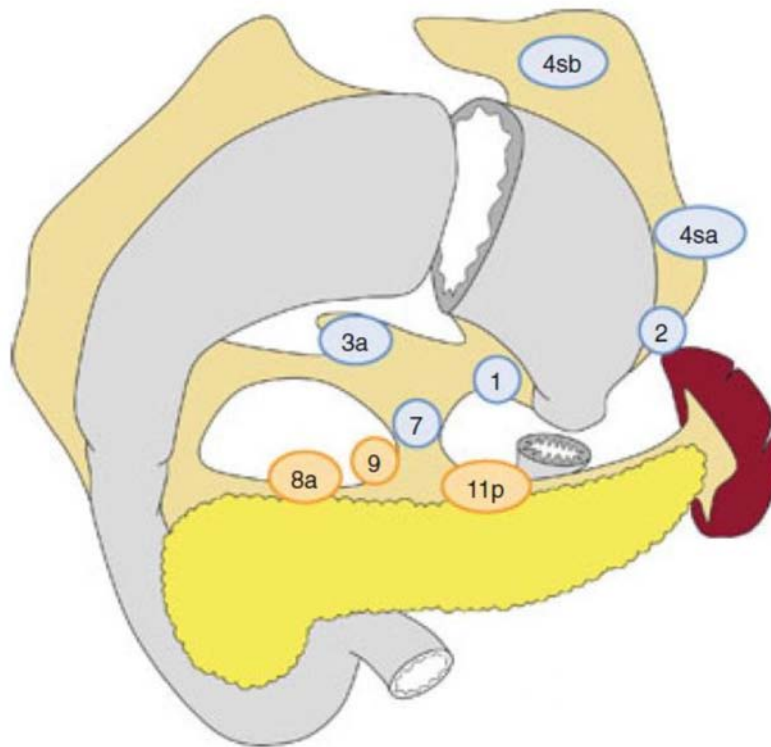


Fig. 4 Lymph node dissection levels in proximal subtotal gastrectomy [17]

Extended LD in larger volumes than mentioned above is classified as D2 +. Its effectiveness remains controversial, therefore it is not recommended for routine use in clinical practice [17].

Gastric cancer classification issued by JGCA (1998) has demonstrated its high efficiency in several clinical studies [9, 19, 20]. LN staging based on the topographical principle laid the grounds for JGCA's classification, which allows us to consider it as anatomical in contrast to a rather mechanistic quantitative approach of UICC classification. This allows reflecting disease propagation and making its prognosis more accurately. In support of this thesis the correlated survival of patients with lesions of various LN groups was demonstrated: in cases with the same number of regional lymphogenous metastases the patients' survival differed depending on lesions of various LN collectors [21]. Thus, localization of metastatically affected regional LN has a probable prognostic value as well as quantity. Thus, according to Y. Noguchi [22], in N0, LN lesion groups 1-6 (N1 according JGCA), LN lesion



groups 7-12 (N2) and LN groups 13-16 (N3), 5-year survival rate came to 85 %, 60%, 25% and 11%, respectively.

Another significant advantage of JGCA gastric cancer classification in terms of practical application is its direct link with the volume of lymph node dissection based on the staging principle of lymphogenous metastasis. It should be noted that according to the Japanese classification the term of “regional lymph node” is defined not only by the lymph node top, but also by the site of the primary tumor in the stomach; UICC classification doesn't provide this differentiation.

And another obvious advantage of classification offered by JGCA lies in the possibility to extrapolate data about regional LN condition into the UICC classification, while the reverse conversion is not possible, which does not allow conducting a comparative analysis in retrospective studies of different clinics.

Western pathologists and surgeons criticize Japanese GC classification mainly for its complexity; plus, in practice the process of precision mapping turns out to be laborious. Yet, the “Eastern” and “Western” GC classifications are on their long-lasting way to “approaching” each other. This tendency can be observed in the last edition of TNM UICC classification and the latest editions of the Japanese gastric cancer treatment guidelines JGCA [17, 18].

For the first time the retrospective analysis results of LD D2 application were published in Japan in 1970 by M. Mine and co-authors. [23]. The authors reported a slight increase in the survival rate among patients with pN0 and a probable growth of the 5-year survival in the group pN + from 10 to 21%. Similar results were received in a study of Y. Kodama [24], who indicated an increase of 5-year survival in the entire group of patients from 33% to 58%.

In the 70's - 80's of the last century Japanese surgeons were actively developing a doctrine of aggressive preventive GC surgery, which was based on the extended (D2), and extra-extended (then so-called D3 LD) LD volumes [25]. At the same time in Europe and the United States the most common LD volume was D0-1 LD. Considering fairly lower incidence rates, European and American surgeons were at the stage of reframing the ideology and mastering the techniques of extended

interventions in GC cases up till the end of the 90s. Eventually, it became a reason for a scientific conflict between the “Eastern” and the “Western” surgical schools: Japanese surgeons determinately used D2 LD in surgical practice, whereas European surgeons insisted on repetitive clinical trials in the European patient population reasoning that certain biological differences of GC are present in the “east” type [26].

One of the most presentable and prospective studies of that time in a European population of patients with GC was a study presented by F. Paccelli with co-authors [27]: the authors reported a probable increase of 5-year survival of 30% (D1 LD) to 49% (D2, 3 LD) in the III stage of GC and from 50% to 65% - of the entire group of patients.

Similar results were obtained by the group of German surgeons supervised by J.R. Siewert during the course of a prospective multicentric trial of nearly 2.5 thousand patients [28]: a probable increase in survival was registered in patients with GC of II-IIIa stages. However, in patients with pN2 (TNM UICC), as well as in cases of tumor invasion of stomach serous membrane on a vast area, D2 LD did not provide any improvement of survival.

However, over the time researchers more and more often noticed the low credibility of non-randomized studies. The results of the first randomized trials published by D.M. Dent with co-authors [29] and C.S. Robertson with co-authors [30] featured high rates of postoperative complications and mortality. However, due to a small number of randomized patients involved in the study, the results couldn't have provided high levels of credibility. The first large-scale randomized multicentric study of the D2 LD efficiency in European populations of patients with GC was carried out in 90s. The study known as a Dutch trial [31] (1078 patients were randomized) was organized by the Dutch group of researchers (Dutch Gastric Cancer Group). At the same time British MRS (Medical Research Society) carried out their own trial [32] (400 patients were randomized). The first results of these studies were preliminarily published in 1997 at the II International Gastric Cancer Congress (IGCC) in Munich. However, the necessity of compliance with full volume of D2 LD dramatically increased the frequency of splenectomies in all groups under the study

(up to 37% according to Dutch protocol and up to 65% - in the UK), and resection of the pancreas (30% in the Dutch study and the 56% - in the British). Apart from that, the study demonstrated a dramatic increase in the number of postoperative complications after D2 LD (from 25% after performing D0-1 in the control group; up to 43% in the Dutch trial, and from 28% to 46% - in the British trial), as well as a growth of postoperative mortality rate (from 4% to 10% in the Dutch trial, and from 6.5% to 13% - in the British trial) [31, 32]. In East-Asian clinical trials, however, the rate of postoperative complications was 17-21% [33, 34]. The postoperative mortality rate after D2 LD in Eastern clinics was also significantly lower compared to European: in the Japanese nationwide registry it was less than 2% [35], in specialized clinics- less than 1% [34] or even a zero [33].

After a 5-year follow-up of European randomized studies the expected increase in survival of D2 LD group was not achieved: 5-year survival in the Dutch trial was 45% in group D1 LD and 47% - in group D2 LD, and in the British trial - 35% in group D1 LD and 33% - D2 LD [36, 37].

Thus, proceeding from the principles of evidence-based medicine and relying on the results of two major Western randomized trials, the European oncology society came up with the preliminary conclusion regarding the ineffectiveness of the extended volume of LD in European populations of patients with GC. However, already in 1999 at the next International Congress on gastric cancer (IGCC) in Seoul, M. Sasako (Tokyo Japan) - a senior consultant of the Dutch trial, presented a detailed analysis of this study and revealed all potential reasons for the absence of a positive result. The summary of this analysis was later published in the New England Journal of Medicine [38]. Yet, despite a good design and detailed statistical analysis, the study had some serious shortcomings which made the results ambiguous, namely:

- A large number of participating surgical centers (about 80 clinics) resulted in an inefficient amount of practical experience obtained by surgeons especially when it came to advanced surgeries they had to perform within the study. Thus, some surgeons performed less than 5 operations of D2 LD throughout the year.

- The lack of surgery standardization (there were no clear criteria of splenectomy or spleen-saving dissection of the 10<sup>th</sup> LN group, instrumental or manual anastomosis, etc.).
- A significant number of surgeons under the study didn't have the specific experience in the issue of extended operations on patients with GC, which not only potentially affected the level of postoperative complications and mortality, but also led to a reduction in LN removal in the course of D2 LD and, consequently, to the reduction of radical surgeries [38].

In contrast to the latter fact, for example, surgeons participating the randomized trial in Taiwan performed minimum 80 operations of D2 LD before the study began. The results of the study revealed a possible increase of survival if extended volumes of LD are performed [39].

The median number of removed LNs is an important indicator of lymph node dissection efficiency. By today, significant geographic fluctuations of this indicator in the performance of D2 LD have been established: from diametrically polar indicators in European randomized trials (in the British study the median number of removed LNs was 17 [32], in the Dutch study - 30 [36]), up to the level of 25-26 LNs in the Western retrospective studies [40, 41], and it reached the point of 54 LNs in Japanese specialized centers [34]. The minimal adequate number of removed LNs in the gastric cancer surgeries according to the requirements of TNM UICC (2009) [18] is 15. This level of LD is provided in the Western retrospective studies in 86% [40] - 95% [41] of patients and in 100% of patients within the Japanese studies [34]. According to J.R. Siwert [28] the efficiency of LD execution can meet the standards of D2 only when min 26 LNs are removed.

An average frequency of metastatic lesions of LNs, group №10 (LNs of splenic hilum) in various tumor sites in the stomach comes to 8.8% and is likely to aggravate the prognosis [42]. The application of splenectomy on principle (for LN dissection of the 10<sup>th</sup> group) didn't prove to be effective in patients with GC up till today. Thus, a small study conducted in Korea by W. Yu and co-authors [43]

demonstrated a tendency to increase survival after splenectomy execution in the course of a surgery, which, however, was not statistically credible. A meta-analysis conducted in 2009 by K. Yang and co-authors [44] also confirmed a feasible increase of 5-year survival in patients with GC after splenectomy execution. According to some other authors [42] the splenectomy execution, apart from the direct tumor ingrowth into the spleen, is necessary only in case of LN lesion of group №4sa. Therefore, despite the fact that LN dissection of the 10th group is regulated by the Japanese gastric cancer treatment, guidelines JGCA (2011) [17] for performing gastrectomy its place and role as a standard stage of D2 LD remains controversial. Most likely, the answer to this question will be obtained soon after the publication of the results of large randomized trial on the efficiency of the Japanese splenectomy in patients with cancer of the upper third of the stomach JCOG 0110, which started in Japan in 2002 [45].

Despite the previous pessimistic results, H. Hartgrink and co-authors [46] conducted a second analysis of the “Dutch material” in 2001. As a result a significant increase of survival in group D2 LD was observed, namely in patients with metastases in LNs of the first stage of metastasis (N1 by JGCA). After 15 years of patients’ observation during the Dutch trial a significant difference in survival in the groups under observation hasn’t been redefined. However, as soon as the most controversial group of patients with splenectomies and resection of pancreatic gland has been excluded from the analysis the 15-year survival rate increased dramatically from 22% in D1 LD to 35% for D2 LD ( $p = 0.006$ ) [47].

In 2013, the results of meta-analysis obtained by 12 randomized controlled major European trials on LD D2 effectiveness were published. Also, it clearly proved the thesis about an increased risk of postoperative complications in carrying out D2 LD and the possible increase of patients’ survival only in the group that did not have splenectomy and resection of the pancreatic gland [48]. Therefore, the latest European oncology guidelines D2 LD offered as a standard surgical procedure but only in highly specialized centers with extensive experience on such surgeries and postoperative care [49].

Therefore, according to the Japanese guidelines on the gastric cancer treatment issued by JGCA (2011) [17], the algorithm of surgical treatment in patients with GC is as follows (Fig. 5).

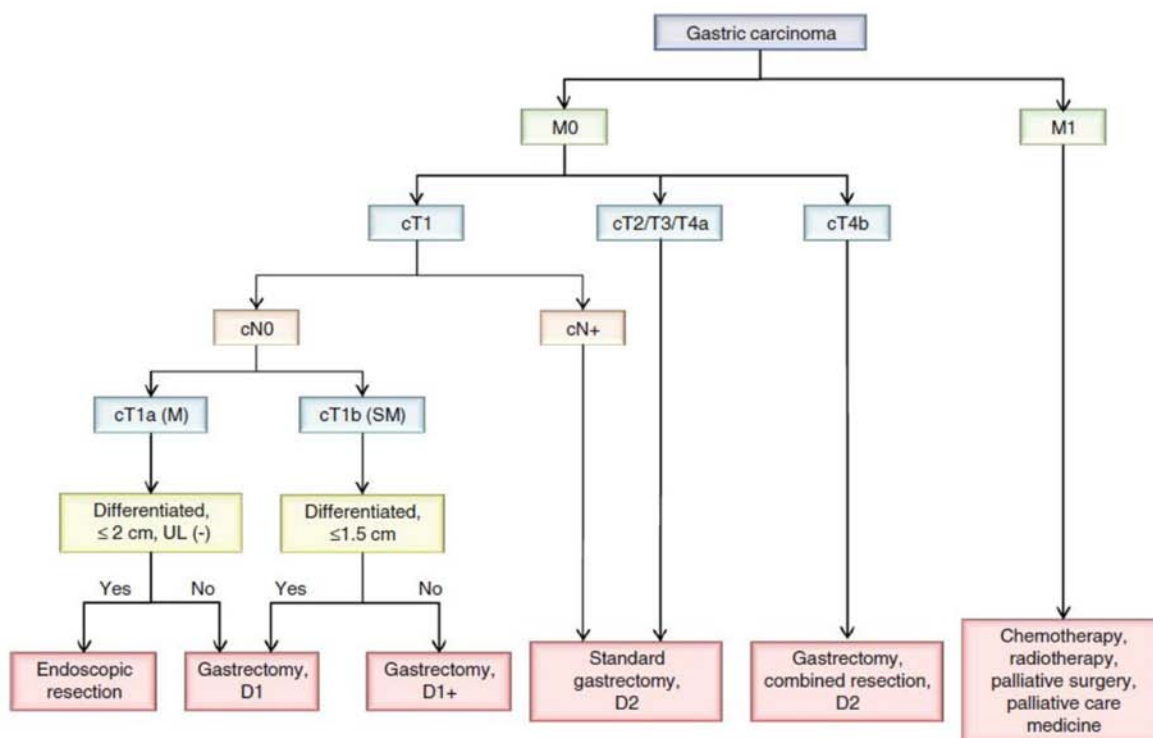


Fig. 5. Algorithm of surgical treatment of patients with GC according to the guidelines provided by JGCA (2011) [17].

For quite a long time the most argued and discussed question on the pages of medical periodicals in the section of gastric cancer surgery concerned the determination of the necessary volume of LD in the surgical treatment of this disease. Today, however, in the light of evidence-based medicine one can observe the results of this complex evolution of views: D2 LD is regarded as an unambiguous standard of GC surgical treatment in specialized centers according to national recommendations in Germany [50], the UK [51] and Italy [52] and also according to the mutual recommendations of the European Society of medical oncologists, surgical oncologists and radiation therapists (ESMO-ESSO-ESTRO) [49]. Such a consensus of the “Eastern” and “Western” surgical schools became possible due to the longstanding scientific and practical search for the ways which would help to improve results of GC surgeries within the evidence-based medicine. So far, in the

western surgical terminology D2 LD is called a standard volume of intervention, whereas an extended operation is a surgery with the D2 + LD execution.

The debate about the effectiveness of extended (D2 + LD) interventions in GC cases remains open today. A well-known clinical study conducted by M. Sasako with co-authors [38] didn't demonstrate an increase in survival after D2 + paraaortic LD has been performed on patients with resectable GC. However, a number of recent studies demonstrated the possibility of increasing survival after the application of the extended LD in a selected group of patients with high risk of metastasis in LNs of the 16th group [53, 54]. However, the question about the effectiveness of laparoscopic D2 LD in GC cases remains undetermined. Today, clinical research known as KLASS-2 trial is being underway. The major objective of this research is to determine the effectiveness of such interventions. Also, the issue of an impact of interventions with D1 +, D2 and D2 + LD on the risk of intraperitoneal progression of GC after surgery [1, 10] remains open.

Therefore, in view of the facts mentioned above, we can claim today that D2 LD might improve the prognosis in European populations of patients with GC, but only in case of an adequate surgical quality of LD execution. As part of the 10th International Congress on gastric cancer (IGCC) in Verona (Italy) in 2013, the former president of the European Society of Surgical Oncology (ESSO) professor C. van de Velde in his expert lecture noted that “the only way to improve the efficiency of surgical treatment of gastric cancer in Europe is to place patients in specialized surgical centers, provide training so that individual surgeons could specialize on the issue of LD D2 and an objective and permanent audit on quality of lymphadenectomy in each surgical center”.

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