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## Gastric cancer; actualities and perspectives of early diagnosis and targeted therapy

Adrian Silaghi

*St. Pantelimon Emergency Clinical Hospital, Department of General Surgery, Bucharest, Romania*

Laura Florentina Rebegea

*Dunarea de Jos University of Galati, Department of Internal Medicine, Galati, Romania*

Daniela Gabriela Balan

*Carol Davila University of Medicine and Pharmacy, Department of Physiology, Bucharest, Romania*

Anca Dumitriu

Stana Paunica

*Carol Davila University of Medicine and Pharmacy, Dan Theodorescu Hospital, Bucharest, Romania*

*See next page for additional authors*

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### **Authors**

Adrian Silaghi, Laura Florentina Rebegea, Daniela Gabriela Balan, Anca Dumitriu, Stana Paunica, Cristian Balalau, Stefăniță Tenea Cojan, Dragos Epistatu, and Vlad Denis Constantin

# Gastric cancer; actualities and perspectives of early diagnosis and targeted therapy

Adrian Silaghi<sup>1</sup>, Laura Florentina Rebegea<sup>2,3#</sup>, Daniela Gabriela Balan<sup>4</sup>, Anca Dumitriu<sup>5#</sup>, Stana Paunica<sup>5#</sup>, Cristian Balalau<sup>1,6</sup>, Ștefăniță Tenea Cojan<sup>7</sup>, Dragos Epistatu<sup>8</sup>, Vlad Denis Constantin<sup>1,6\*</sup>

<sup>1</sup> St. Pantelimon Emergency Clinical Hospital, Department of General Surgery, Bucharest, Romania

<sup>2</sup> Dunarea de Jos University of Galati, Faculty of Medicine and Pharmacy, Department of Internal Medicine, Galati, Romania

<sup>3</sup> St. Ap. Andrei Emergency Clinical Hospital, Department of Radiotherapy, Galati, Romania

<sup>4</sup> Carol Davila University of Medicine and Pharmacy, Department of Physiology, Bucharest, Romania

<sup>5</sup> Carol Davila University of Medicine and Pharmacy, Dan Theodorescu Hospital, Bucharest, Romania

<sup>6</sup> Carol Davila University of Medicine and Pharmacy, Department of General Surgery, Bucharest, Romania

<sup>7</sup> Craiova University of Medicine and Pharmacy, Romania, Department of Surgery, Craiova, Romania

<sup>8</sup> Carol Davila University of Medicine and Pharmacy, Department of Radiology, Bucharest, Romania

# These authors contributed equally to this work and thus share first authorship

## ABSTRACT



Gastric cancer is an extremely aggressive form of malignancy that, if left untreated, is life-threatening. Improved survival rates depend on early detection of the disease, as well as on the combination of different forms of treatment (surgery, chemotherapy, radiotherapy, immunotherapy, etc.). Screening methods have brought real benefit in early detection of malignancies, but many cases are still diagnosed at advanced stages. The current study is a review related to actualities and perspectives of early diagnosis and targeted therapy of gastric cancer. After an extensive review of the literature, epidemiological, diagnostic and treatment data are presented. The open surgical approach is used in emergency centers or with a low surgical activity, while the minimally invasive approach (laparoscopic, robotic) is possible in large centers dedicated to the treatment of gastric cancer. In the near future, new diagnostic and therapeutic tools are expected to appear, not only to cure cancer definitively, but also to be able to prevent it, if possible, without radically changing the lifestyle of the population.

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**\*Corresponding author:**

Vlad Denis Constantin,

Carol Davila University of Medicine and Pharmacy, Dionisie Lupu St. No. 37, St. Pantelimon Emergency Clinical Hospital, Bucharest, Romania

E-mail: [constantindenis@yahoo.com](mailto:constantindenis@yahoo.com)

## Introduction

Gastric cancer (GC) is one of the most aggressive forms of malignancy [1,2]. The emergence of GC is conditioned by the existing interconnection between genetic, epigenetic, systemic and environmental factors, so its therapeutic management requires a multidisciplinary approach. The development of the disease is carried out in several stages, the final result being a series of changes that favor the growth and development of malignant cell lines (secondary to the release of mediators that influence cell adhesion, the translation of genetic material and the action of various specific kinases). The presence of GC-specific cells or molecules can be detected by plasmapheresis, real-time polymerase chain reactions or spectrophotometry, the clinical significance being the transformation of normal to

malignant tissue, some of which can be used as markers of progression or diagnosis in gastric cancer [3,4].

Good survival rates are closely related to both early detection of the disease and the combination of different forms of treatment (surgery, chemotherapy, radiotherapy, immunotherapy, etc.). Although screening methods have brought a great benefit in the early detection of the disease, many cases are still diagnosed in locally advanced stages. In such cases, the basic treatment is surgical, the type of operative procedure, the number of nodes harvested and examined, as well as the resection margin (which must be negative) being important in the postoperative prognosis [5-8].

The most widely used classification of gastric cancer is that developed by Lauren with intestinal and diffuse adenocarcinomas. In addition, multiple characteristics are

described such as genetic, morphological and epidemiological elements, all having a marked impact in terms of the surgical-oncological approach [4]. Rare forms of gastric tumors are represented by sarcomas, lymphomas or gastrointestinal stromal tumors, etc. [5,6].

The current study is a review that focuses on new methods of diagnosis and targeted treatment, the advantages and disadvantages of different approaches or techniques used, and the perspectives for diagnosis and treatment of this life-threatening condition.

## Discussions

### *Epidemiology*

Each year, approximately 1 million new cases of gastric cancer are diagnosed, along with 782,685 deaths associated with it. It is thus the 5th most common cancer diagnosed in 2018, representing 5.7% of the total. Mortality related to gastric cancer ranks 3rd after lung and colorectal cancer [6-9].

The incidence of gastric cancer increases with age and varies by sex. It is 2 times more common in men than in women, being the 4th most common in men and the 7th in women [10-12].

Globally, there has been a decline in gastric cancer mortality, but with wide variation in incidence and mortality rates [9,10]. At the end of 2018, 86% of new gastric cancer cases were identified in patients residing in countries with a high development status. It is probably the consequence of *Helicobacter pylori* (HP) infection and especially of the virulent strains found in certain geographical areas such as South and East Asia, where the population density and degree of development are high [11,12]. The highest reported incidence was on the Asian continent, especially in the Eastern region (32.1/100,000 inhabitants), followed by Central and Eastern Europe (with values of 17.5/100,000 inhabitants), while the lowest values have been observed in Africa with approximately 5 cases per 100,000 inhabitants [11].

In terms of mortality, there was a decrease due to the early diagnosis of gastric cancer in countries with a high incidence of the disease, such as Korea and Japan, being the first countries where the decrease was marked, the other countries following the same trend but much more slowly [13]. The highest mortality rates are recorded in Central and Eastern Europe, along with Asia, and the lowest in North America [11].

Risk factors in the development of gastric cancer are represented by chronic HP infection, smoking, excessive alcohol consumption, obesity, poor diet and genetic factors [14].

HP infection is the leading cause of gastric cancer, being responsible for 89% of cancers placed in the distal portion of the stomach [15]. It occurs mostly in childhood through the consumption of foods containing HP and

persists until it is eradicated by treatment [16]. Different HP strains have a distinct ability to cause gastric cancer. The presence of the gene associated with the oncogenic cytotoxin (CaG) and associated antibodies leads to an increase in neoplasms with gastric extracardial localization [17]. The presence of HP strain variability also explains the uneven distribution of gastric cancer incidence globally, mostly in accordance with the presence or absence of the CagA gene associated with phosphorylation sites from the tyrosine kinase pathway [18]. The CagA EPIYA-D HP strain found in East Asia has an ability to stimulate SHP2 phosphatase twice as strongly as the CagA EPIYA-C found predominantly in the western regions of the continent [19].

Smoking is one of the predisposing factors for the occurrence of gastric cancer, there is a causal relationship between them [20], so exposure to cigarette smoke is associated with an increased risk of developing gastric cancer at cardiac level [21]. This fact was demonstrated by an analysis of 10,290 gastric cancer patients and 26,145 patients enrolled in the control group, with smokers having a 25% higher risk of developing this pathology compared to non-smokers. The risk of gastric neoplasia determined by cigarette smoke correlates with the number of cigarettes smoked per day and the duration of exposure. This fact is supported by the decrease in the incidence of GC after smoking cessation, which may lead to a level of risk similar to that of the non-smoking population after 10 years of abstinence [22].

A body mass index higher than 30 kg/m<sup>2</sup> may be associated with a moderate risk of gastric cancer, especially of the cardiac region [23,24]. The non-Asian population is most affected compared to Asians who have a 3% higher risk of developing gastric neoplasia than a person with a body mass index of 25 [25].

A diet high in processed meat, regardless of its nature, may increase the risk of developing non-cardiac gastric cancer due to the amount of nitrates and nitrites, especially N-nitrosodimethylamine (NDMA). Its excessive consumption can lead to a 34% increase rate of developing gastric cancer compared to those who have a balanced diet low in food additives. The degree of risk correlates with the amount consumed, so any intake above 0.12 ug/day may increase the frequency of gastric cancer [26,27]. In addition to processed meat, the level of salt can lead to the appearance of gastric cancer through lesions of the mucosa determined by a strong osmotic activity and through increased levels of gastrinemia, which will lead to cell proliferation [28], a fact confirmed by several studies [29,30].

Among the protective factors, an increased intake of fresh fruit is one of the few foods whose protective effect seems to be confirmed in both cardiac and non-cardiac gastric cancers [30,31].

Alcohol consumption can cause changes in the control mechanisms of cell proliferation, including at the level of

the gastric mucosa [32,33], so that for every 10 g of pure alcohol/day, an increase of approximately 7% of the incident is recorded [34]. Among the types of alcohol consumed, the greatest risk was determined by beer and spirits, which caused the disease to occur especially at the extracardial level [35].

Administration of NSAIDs, even non-selective ones, can be considered a protective factor for the occurrence of gastric cancer, since large amounts of cyclooxygenase-2 are found in gastric tissue [36,37]. Thus, every 2 years of NSAID consumption, the risk of its occurrence decreased by 11%, especially for the disease with non-cardiac location, thus emphasizing the correlation between dose and risk [14].

Statins used to improve lipid metabolism disorders and decrease cardiovascular risk can be considered protective factors in the occurrence of gastric cancer. The beneficial effects are due to their antiproliferative, proapoptotic, antiangiogenic and immunomodulatory function, their use being beneficial if consumed for more than 2 years leading to risk reduction rates of up to 27% [38].

Other factors involved in the occurrence of gastric cancer are represented by genetic ones, so that in the case of a family where there was a patient with such a disease, the risk of development is 10 times higher for relatives of the first degree compared to the general population. Hereditary syndromes such as Lynch, Li-Fraumeni, Peutz-Jeghers syndrome are described, which are transmitted in an autosomal dominant/recessive manner and can lead to diffuse gastric cancer [39,40].

#### Diagnosis

Early detection of gastric cancer has resulted in a marked decrease in deaths and a 5-year survival rate of over 90%. These data are reported by countries where rapid and effective means of early diagnosis have been developed, such as Japan, where the GC mortality rate five years ago was below 10% [41]. Classical diagnostic markers such as carcinoembryonic antigen (CEA), carbohydrate antigen (CA) CA19-9, CA 72-4, CA125, CA 24-2, alpha-fetoprotein and pepsinogen are nonspecific and none of them are characteristic of cancer gastric [42,43]. Consequently, it is necessary to identify other molecules that could determine the early onset of malignancy, preferably by cheap and quick methods if possible.

Relatively useful proteomic markers in the diagnosis, monitoring and prognosis of gastric cancer are represented by CA72-4, CA19-9, CEA. However, their low sensitivity and specificity make it impossible to use them as a screening method [43,44]. To achieve a better diagnostic performance, it is necessary to add another marker, such as thymidine kinase 1 (TK1), which reveals the presence of intense cell proliferation. Through comparative studies, the sensitivity and specificity of this combined method was higher than the single use of classical markers [45,46].

Measurement of serum levels of pepsinogen and gastrin 17 (G-17) as markers of the onset of gastric atrophy, a condition known as potential premalignancy, has led to a faster diagnosis of gastric cancer [47]. Moreover, an analysis of the ratio between pepsinogen 1 and 2, together with the serum level of G-17 and anti-HP antibodies, represents an important tool that can be used to evaluate patients at very high risk of developing gastric neoplasia, due to the presence an advanced premalignancy status [48].

Another series of molecules that can be considered as serological markers in patients with gastric cancer are serum N-glycans and fucose, both of which have the ability to differentiate very precisely healthy patients but with high proliferation rates in the gastric mucosa. However, large groups of patients are needed to accurately determine their sensitivity and specificity [49,50].

Alteration of the expression of some oncogenes can be used as a marker for the early diagnosis of gastric cancer. Xeroderma pigmentosum group G/excision repair cross-complementing group 5 (XPG/ERCC5) is an enzyme complex involved in the repair of the human genome secondary to its instability. It has a high expression in gastric malignancy compared to inflammatory diseases, the level of expression being correlated with the development and progression of the disease [51].

The use of gene microarray techniques led to the identification of a cellular receptor structurally similar to epidermal growth factor containing two foliostin-like domains (TMEFF2) and whose genome-wide expression is very low in gastric cancer patients, being correlated with advanced stages, early metastases and large tumor volume. These consequences are due to the inability to block the proliferation and apoptosis of neoplastic cells secondary to their inactivation [42]. HP can alter TMEFF2 gene expression by interacting with the STAT3 domain, promoting aberrant, uncontrolled proliferation and inhibiting cell apoptosis [52,53].

By correlating several genetic panels that can be harvested from plasma, gastric cancer patients can be identified with 95% accuracy, 92% sensitivity, and 96% specificity. Such factors are represented by purine-rich element binding protein B (PURB), structural maintenance of chromosomes 1A, underexpression of DENN/MADD domain containing 1B (DENND1b) and programmed cell death 4 (PDCD4) [54].

MiRNAs are RNA chains containing between 19-25 nucleotides involved in various cellular functions such as differentiation, proliferation and apoptosis, acting as oncogenes or tumor suppressor factors. They are found in variable proportions in tissues including solid tumors [55]. In patients with gastric cancer, the serum level of miRNA-21 was identified with high concentrations, having a predictability rate of 90%, while the level of CA199 together with CEA reaches 50%. The serum level can be

correlated with the stage of the disease, significant differences being found between stages I and IV [56].

The circulating levels of miR-196a and b are detected in high amounts in gastric cancer patients compared to healthy individuals. Postoperatively, serum miR-196a level decreased, and increased miR196a/b ratio correlates with metastatic cancer, advanced stages, and shorter survival. The sensitivity and specificity of this marker is much higher compared to the combination of CEA and CA19-9 [57].

The development of miRNA panels composed of miR16, miR-25, mir92a, miR 451, and miR486-5p can differentiate gastric adenocarcinoma patients from healthy subjects and also describe the location whether it is cardiac or non-cardiac [48]. All these panels are associated with high sensitivity and specificity, the only drawback of which being the small group of patients involved in the studies. They are needed to be validated on large groups, but the costs of processing large samples of patients are currently unaffordable [47].

LncRNAs are transcription factors longer than 200 nucleotides that did not result in the formation of a protein, being involved in various cell cycle processes [58,59]. Having a high stability in different fluids such as urine, serum, gastric secretion, their concentration can be increased in various neoplastic diseases, a significant correlation being observed between the stages of the disease and its concentration [60]. The serum level of H19 can be a potential biomarker of gastric cancer due to the increased sensitivity and specificity [61], the main function being the stimulation of cell proliferation and the inhibition of apoptosis [62], so that the plasma concentration is increased in tumors over 5 cm, while the serum level decreases postoperatively [47].

Long intergenic non-protein-coding RNA 152 (LINC 00152) is expressed in a high amount in gastric cancer patients compared to healthy controls [63]. Unlike LINC00152, AA184084 can be identified in the gastric juice of patients with gastric tumors. The plasma level is correlated with the degree of tumor invasion; following gastric resection, a decreasing trend can be observed starting from the 15th postoperative day [64,65].

Circular RNA chains were first identified in RNA viruses, later being identified in eukaryotic cells, having the role of controlling the expression of stable sequences of genetic material through the interaction with miRNA [66]. Starting from this interaction between miRNAs and CircRNAs, they have been identified in solid tumors acting synergistically to stimulate the proliferation of cancer cells and their ability to metastasize. Recent studies have shown an aberrant expression of circRNA compared to healthy patients. An advantage of this special category of genetic material is its ability to resist RNase and the strongly acidic environment of gastric juice [47].

Circulating tumor DNA is the genetic material released in the plasma of neoplastic patients secondary to cell destruction and can be identified as a marker in the initial stages of the disease. The amount of genetic material increases with the stage of the disease [47]. Higher plasma levels may correlate with a severe degree of vascular invasion, higher rates of recurrence and peritoneal invasion, the survival prognosis for these patients being usually less favorable [67]. The main disadvantage of this diagnostic method is the need for high sensitivity to obtain a quality investigation. New techniques such as quantitative PCR and digital droplet PCR allow plasma identification of genetic material to be identified in patients with gastric cancer. The results obtained are relatively similar to those of a biopsy, but with the advantage of collecting a single vial of peripheral blood [47].

#### *Endoscopic diagnosis*

Endoscopic diagnosis of gastric cancer, together with microscopic examination of the collected sample, is the main method for diagnosing gastric cancer, being also used as a screening method for high-risk populations [68,69]. The most widely used endoscopic method for detecting gastric cancer and premalignant lesions is white light endoscopy, which has the ability to identify discolored areas on the gastric mucosa, as well as ulcerative or polypoid lesions [70]. The sensitivity for this method ranges from 29% to 72% for both low-grade dysplasia and high-grade and advanced disease, so it is necessary to use other technical means to detect and identify as many lesions as possible.

Narrowband band imaging is a form of virtual endoscopy that uses a light filter to separate the white light beam into two different wavelengths. This determines the amplification of the relief of the gastric mucosa with a better highlighting of the vascular pattern at this level. Compared to white light endoscopy, the method can detect premalignant lesions at a much higher rate (up to 40% more lesions) [71], with a sensitivity of up to 69% and a specificity of up to 91% [72].

High-magnification endoscopes use a system of lenses that have the ability to magnify images up to 150 times [73]. By combining the optical magnification system with narrowband imaging, remarkable results were obtained, detecting premalignant lesions with a sensitivity of 80-89% and a specificity of 93-96% [74,75]. These data were also confirmed by a meta-analysis study performed on a group of 2171 patients, which obtained similar results [76]. A great advantage of this technique is that it can accurately detect the endoscopic resection margin, the accuracy being 97.4-98.1% [65], much better results than other techniques such as chromoendoscopy based on the staining of various suspicious lesions during the procedure [77,78].

Confocal laser endomicroscopy uses a laser that sends a beam of light to the gastric mucosa, which is later reflected and captured by a detector that will transform the

light signal into digital images [79]. The sensitivity and specificity of this method reaches values of over 95%, but with the disadvantage of the increased cost secondary to the high-performance equipment and the long training time of the technicians [80].

Artificial intelligence systems can be connected to this diagnostic method, being able to learn to recognize different vascular patterns and cell distribution, thus leading to better recognition of premalignant and malignant lesions. The results obtained by connecting such systems can reach the level of an experienced specialist, but with the advantage of a fast-learning time and with a sensitivity of 95.4 [81].

Surgical treatment remains the only modality of curative treatment, which aims to remove the tumor along with the adjacent invaded lymph nodes, especially in stages I and II [82,83]. However, chemotherapy or immunotherapy can be used as neoadjuvant and adjuvant treatment with a marked increase in survival, especially for stages II and III [84]. The chemotherapy regimen used by most centers is currently based on docetaxel, 5-FU, leucovorin and oxaliplatin (FLOT), which has good results with a median survival of 50 months.

Regarding the metastatic stage of malignant disease, a separate approach based on chemotherapy and individualized treatment with immunotherapy or enrollment in clinical trials. First-line treatment is based on platinum derivatives such as oxaliplatin and a cytotoxic agent such as 5-FU, with or without Trastuzumab if there is expression of HER2 receptors or other monoclonal antibodies depending on the genetic characteristics of the tumors [85].

Tyrosine kinase inhibitors are a series of pharmaceutical products with the role to block the phosphorylation process at the cellular level, thus inhibiting cell proliferation processes through interaction with HER2, EGFR, VEGF and MET receptors [86,87]. Among these, imatinib, a blocker of BCR/ABL, c-KIT and PDGFR, has been tested in the treatment of stromal tumors of the digestive system and for metastatic cases of gastric cancer, showing increased efficacy and good clinical response.

Sunitinib, a selective VEGF inhibitor administered to patients with gastric cancer, did not show a significant clinical benefit compared to standard treatment [88]. Its inefficiency may be due to mutations occurring at the level of the KIT gene, its intra-lysosomal sequestration with subsequent degradation, or due to marked cytoplasmic efflux [89,90].

Vandetanib is a multikinase inhibitor with predominant action on VEGF-R factor that, in combination with paclitaxel, carboplatin, and 5-FU, led to disease-free progression rates of over 3.7 years compared to standard treatment for early-stage cases of the disease [91].

An alternative pathway for the development of malignant process cells is represented by the modification of the cytoskeleton, which could lead to apoptosis, an effect especially evident in forms of poorly differentiated gastric cancer. The main target of this type of treatment is cytoskeleton proteins such as tubulins, dynamins, myosin and kinesins. T900607 is a selective tubulin inhibitor that irreversibly binds to the site of action of colchicine and is being investigated as a treatment for gastroesophageal junction cancers [92,93]. Among cytoskeletal proteins, microtubule-associated proteins (MAPs) could be inhibited together with FAM89, both of them being overexpressed in gastric cancer and thus lead to tumor regression and healing, a fact that remains to be investigated in large groups of patients [94].

Cellular DNA repair is a complex process required for cellular survival and may be the target of individualized treatment. In gastric cancer, ATM, BRCA1, and ATR proteins are mutated in 14–20% of cases, leading to a high mutagenic capacity and the appearance of the cancerous phenotype [95]. Poly (ADP-ribose) polymerase is an enzyme involved in numerous cellular processes, such as chromatin binding and recruitment of genetic material repair proteins [96]. The development of its inhibitors leads to decreased DNA repair capacity, especially in BRCA mutant cells, thus leading to synthetic lethality [97,98]. Olaparib, a PARP inhibitor, was tested in the Asian population with gastric cancer, but did not obtain statistically significant data on survival rates. Also, the association with paclitaxel led to the same results, but with a trend of disease evolution for patients who had low ATM activity [99].

PD1 is a marker found on T cells and has a role in identifying malignant cells, having the ability to bind to PDL1 and to induce apoptosis. PD1 inhibition with nivolumab increased progression-free disease by 12 months, being a promising immunotherapy option in gastric cancer [100,101].

Another way to eliminate neoplastic cells is through induced autophagy, where BENC1, ATG-like proteins, UVRAG, p62, parkin, lamp2 form a complex that initiates autophagy by receiving cell signals through the mTOR pathway. In patients with gastric cancer, the mTOR pathway is active in 60% of cases, which causes a reaction favoring cell survival and thus leading to a poor prognosis [102]. This fact was confirmed in some poorly differentiated cancers that are sensitive to the inhibition of this pathway. Administration of Everolimus, Temsirolimus, confers a survival benefit on administration [103] and is recommended for advanced cases that have not responded to sunitinib.

#### *Surgical approach to gastric cancer*

Following the discoveries made in the occurrence and development of gastric tumors, surgical or endoscopic

resection is the only curative approach. The surgical approach can be performed both open and laparoscopically or robotically, but with better results in terms of quality of life and the rate of intra- and postoperative complications [104].

Regardless of the minimally invasive or open approach, a number of general principles should be followed. The length of the resection should create a negative resection margin compared to the tumor cells, which depends on the size and location of the tumor, as well as histological type. The ideal distance between the tumor margin and the macroscopically apparent residual tissue is considered to be between 3-5 cm (depending on the pathological appearance of the tumor) but recent studies have suggested that adjuvant treatment can achieve the same oncological outcome in terms of survival with a resection marginal of only 1 cm [105,106].

Regardless of tumor location, total gastric resection has long been the standard procedure. For proximally located tumors, proximal and total gastrectomy were compared, resulting in similar survival and progression-free disease interval [107]. The only differences between the 2 approaches were distant complications such as esophageal reflux disease [108,109]. Regarding the distal localization of tumors, by comparing total gastrectomy with subtotal gastrectomy, relatively similar results were found. Thus, similar rates were obtained in terms of mortality and associated 5-year survival, but with lower rates of wound infection, anastomotic fistula, and better quality of life in the subtotal gastrectomy group [110].

Cardiac localization of a gastric tumor often requires the formation of a supradiaphragmatic anastomosis [111]. This allows for a proximal gastrectomy, a total gastrectomy, or an esophagogastrectomy with proximal cervical anastomosis. Comparing these three methods, there is no difference in 5-year survival if a resection margin of 4 centimeters is obtained for the stomach and 6 centimeters for the esophagus, respectively [112].

Reconstruction after resection can be approached using various techniques. The oldest, described by Billroth in 1881, was the most commonly performed so far, but with higher rates of reflux gastritis compared to Roux-en-Y [113,114], the latter now being the preferred method of reconstruction following a total gastrectomy [115].

When the tumor extends to adjacent organs, a more aggressive approach is required during surgery, often involving splenic, pancreatic, or duodenal resection. Studies conducted on in small groups of patients with good functional status, low number of invaded lymph nodes and the ability to tolerate perioperative chemotherapy showed better survival results compared to those who underwent only gastrectomy [116,117]. However, applying this method to larger groups of patients led to increased mortality and morbidity rates, longer hospitalization, and without a statistically significant change in survival terms [118].

Gastric cancer is considered a lymphophilic malignancy, the main source of metastasis being the lymphatic system. One of the goals of gastric cancer surgery is to remove tumor-related nodal stations during resection, which can improve survival and achieve a favorable operative prognosis [119,120].

D2 lymph node dissection is the standard therapy for locally advanced cancer. For subtotal gastrectomy, resection of stations 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p and 12 is required, while for total gastrectomy, all lymph node stations 1 to 7, 9, 11d, 11d, 10 and 12a should be removed [121,122]. The benefits of this resection include accurate staging and removal of affected lymph nodes, resulting in a lower rate of local recurrence [123].

The optimal number of lymph nodes to evaluate is still a matter of debate. For a minimal evaluation, at least 10 regional lymph nodes should be investigated [124]. The American Joint Committee on Cancer does not define an exact number, but the European, Korean, and Japanese committees recommend that the number should exceed 15 lymph nodes [125,126]. An Italian study showed that removal of more than 25 lymph nodes leads to an increase in postoperative mortality of up to 3.5% [127].

The results of radical surgery should be guided by two fundamental principles: locoregional control and clinical benefit. D2+ resection is defined as D2 resection combined with removal of station 13 and those with retropancreatic location and station 16, indicated in specific cases [128]. Follow-up of patients with D2 and D2+ resection showed that patients with duodenal involvement and D2+ resection had statistically higher survival rates (61.5% vs 20%) [129].

#### *Laparoscopic treatment*

The laparoscopic approach to a gastrectomy was first performed in 1994 by Kitano and colleagues [130] and has become the most widely used minimally invasive method for the surgical treatment of gastric cancer, especially widespread in countries such as Japan and Korea [131]. Regardless of the technique chosen, the principles remain the same, including achieving complete resection with negative microscopic margins. Patients suitable for minimally invasive techniques are those with a low body mass index, and few comorbidities such as cardiopulmonary conditions that could be exacerbated by the presence of pneumoperitoneum and early stages of the disease. In addition, preoperative surgical anatomic assessment is required, as vascular malformations can cause difficulties during dissection [132]. From a technical standpoint, the laparoscopic approach is more challenging due to the complexity of lymph node dissection, which can be problematic in cases of large tumor resections. Nonetheless, various centers in Asian countries have published studies showing no differences in terms of safety and degree of oncological radicality achievable with these



procedures [133]. Kinoshita et al. conducted a multicenter study evaluating 610 randomly assigned patients in two groups, laparoscopic/open approach, and the 5-year results showed similar survival and recurrence rates [134]. Compared to open approach, laparoscopic approach leads to longer operating times of up to 260 minutes, but with lower blood loss and reduced rates of airway infections in the first 30 days [111], while the number of resected lymph nodes in open dissection is higher [135].

In addition, preoperative surgical anatomic evaluation is required, as vascular malformations may cause difficulties during dissection [132]. From a technical point of view, the laparoscopic approach is more difficult due to the complexity of lymph node dissection, which can be problematic in cases of large tumor resections. However, various centers in Asian countries have published studies showing no differences in safety and degree of oncological radicality that can be achieved with these procedures [133]. Kinoshita et al. conducted a multicenter study that evaluated 610 patients randomly assigned to two groups, laparoscopic and open approach, and the 5-year results showed similar survival and recurrence rates [134]. Compared to the open approach, the laparoscopic approach leads to lower blood loss and reduced rates of respiratory tract infections in the first 30 days, but with longer operative times of up to 260 minutes, while the number of resected lymph nodes in open dissection is higher [135].

Robotic approach can also be an option in gastric cancer treatment, yielding very good results with a mortality below 1% and morbidity below 13%. In a study which included 100 patients, complete resection was achieved for all patients, with an average of 36.7 resected lymph nodes [136]. Compared to the laparoscopic approach, the use of robotic technology leads to longer operating times but with less blood loss, without altering the hospitalization period, mortality, morbidity, survival, or local recurrence rate. The major disadvantage is the associated cost and the extended training time for specialists. The learning curve for early-stage gastric cancer cases can extend up to 90 cases; in many Western centers, less than 20 gastrectomies are performed annually. For difficult cases (obese patients, those with previous surgeries, elderly patients with associated comorbidities), the learning curve can extend up to 100 cases [136].

## Conclusions

Recent discoveries in the serological and imaging diagnosis of gastric cancer are extremely valuable because they can detect stomach malignancies early. However, a definitive diagnosis still requires microscopic evaluation of biopsy specimens. Endoscopic methods play a crucial role in the diagnosis of gastric cancer, with techniques such as narrow-band imaging, high-magnification endoscopy, confocal laser endomicroscopy, and AI-enhanced analysis

showing promise in improving lesion detection and recognition. Surgical treatment remains the primary curative approach, with principles such as negative resection margins and lymph node dissection crucial for better results. D2 lymph node dissection is the standard for advanced cancer cases. Laparoscopic and robotic approaches have gained importance for gastrectomy, with laparoscopy being widely adopted in Asian countries and robotic surgery showing advantages despite higher costs.

The traditional approach remains relevant in emergency centers and low surgical volume settings, while the minimally invasive approach is best suited for large centers dedicated to the treatment of gastric cancer, given the steep learning curve and comparable outcomes between the two techniques.

## Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

## Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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