Updates in Surgery

Giovanni de Manzoni
Franco Roviello *Editors*

# Gastric Cancer: the 25-year R-Evolution



# Updates in Surgery

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Giovanni de Manzoni • Franco Roviello
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# Gastric Cancer: the 25-year R-Evolution

Springer

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# Foreword

During the last 25 years, gastric cancer surgery has undergone a number of technical evolutions, concept progressions, and outcome improvements. This has resulted not only from better patient stratification, more efficient multidisciplinary management, and, no doubt, the revolution and evolution of minimally invasive surgery, but also from refinements in surgical approach and the experiences of dedicated centers.

All these aspects and much more have been deeply examined and magisterially illustrated in the present volume that I have the privilege to introduce. It has been for both the Editors an invaluable opportunity to share with the surgical community their extraordinary experience and ideas in the field, combining a long-standing tradition of prestigious surgical schools with a far-sighted view of the future developments.

The structure of the book reflects the lengthy experience of the Editors and Authors and their deep knowledge of the topic, giving us the opportunity to be brought up to date on the results and evidence acquired while sharing the most important trends and innovations in the field.

As the President of Italian Surgeons, I wish to express my deep gratitude to the Authors for this fantastic feat so that, looking at the final results of this scientific endeavor, the words that easily come to my mind are that, without any doubt, the esteemed Colleagues Professor de Manzoni and Professor Roviello have truly honored the Italian academic tradition through the very high scientific quality of this monograph.

Catania, Italy
September 2021

Francesco Basile
President
Italian Society of Surgery

# Preface

Gastric cancer is undoubtedly among the most heterogeneous gastrointestinal neoplasias both from the clinical and morphological-molecular points of view.

The drafting of this book has not only involved the experience of Italian surgeons who have been dealing with gastric cancer for years but also integrated the knowledge of other national experts such as oncologists, molecular biologists, pathologists, endoscopists, and radiologists, who dedicate a large part of their working life to the study of gastric cancer.

The content of this work embodies the philosophy of the holistic approach to gastric cancer. Indeed, nowadays, the surgeon who treats this disease cannot ignore the essential knowledge dispensed within the present volume, when selecting the most appropriate multimodal treatment in gastric cancer for each patient based on the latest evidence available in the literature.

The entire volume culminates in the chapter *Gastric Cancer: Synopsis of Treatment Indications*, which offers practical guidance for the clinical challenges of everyday practice, leaving the reader the opportunity to explore the various topics covered more in detail in the dedicated chapters.

It was a pleasure and an honor to coordinate the experience of the Italian Research Group for Gastric Cancer (GIRCG), which matured over the past twenty years, also in drafting this book. A special thanks goes to the Society of Surgery that allowed us to bring this work to life.

Verona, Italy
Siena, Italy
September 2021

Giovanni de Manzoni
Franco Roviello

The original version of this book was revised: Copyright Year has been updated. The correction to this book is available at https://doi.org/10.1007/978-3-030-73158-8_40

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**Part III Treatment**

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# Part I

# Epidemiology, Pathology, and Diagnosis

# Epidemiology and Risk Stratification in Gastric Cancer

1

Lorena Torroni, Roberta Vesentini, Emanuele Crocetti, and Giuseppe Verlato

## 1.1 Incidence and Mortality of Gastric Cancer

Gastric cancer (GC) ranks fifth for incidence and third for mortality among cancers worldwide. With over one million new cases (n = 1,033,701) and 782,685 deaths in 2018, GC accounts for 5.7% of all cancer incidence and 8.2% of total cancer mortality [1]. Considering that death occurs in about 75% of new cases, it can be inferred that the case fatality rate is high.

GC affects more men than women: in 2018, a total of 683,754 new cases and 513,555 deaths were recorded among men, and 349,947 new cases and 269,130 deaths among women. Accordingly, the age-standardized incidence and mortality rates are more than double in men (15.7 new cases and 11.7 deaths per 100,000 person-years) compared to women (7.0 new cases and 5.2 deaths per 100,000 person-years) [2].

The incidence of GC dramatically increases with age, from 0.58 per 100,000 person-years under 40 years to 98.5 over 70 years in 2020. It is more common among women below 40 years, and in men thereafter. The trend is similar when considering only the European region (Table 1.1) [3].

In the world, the age-standardized incidence rates of GC vary considerably, with maximum levels in Eastern Asia (Japan, South Korea, China, with 22.6 new cases among males per 100,000 person-years), Central/Eastern Europe (22.7) and South/Central America (12.1), especially along the Pacific coast, and minimum levels in

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**Table 1.1** Incidence of gastric cancer in the WHO European region in 2020, according to Globocan [3]

| | Total cases | | Crude incidence rate per 100,000 person-years | |
|---|---|---|---|---|
| Age | Men | Women | Men | Women |
| 0–39 years | 1167 | 1544 | 0.5 | 0.7 |
| 40–54 years | 11,123 | 6199 | 11.9 | 6.5 |
| 55–69 years | 41,574 | 19,520 | 53.6 | 21.8 |
| >70 years | 45,825 | 34,472 | 106.9 | 52.5 |
| Total | 99,689 | 61,735 | 22.0 | 12.8 |

Australia/New Zealand (10.5), North America/Northern Europe (10.3) and Africa (2.6) [4]. According to the World Health Organization "GLOBOCAN" monitoring system (2018), 74.5% of new diagnoses of GC and 74.7% of deaths from the disease worldwide have occurred in Asia; in particular, China alone contributes to more than half of cases. The different incidence, as well as the different clinical-pathological presentation between the Asian and Western populations, are suggestive of different pathogenesis and different underlying biological, environmental, and nutritional risk factors [1].

Thanks to survival improvement, nowadays it is possible to describe not only the cancer's incidence and mortality, but also its prevalence. In 2018, a total of 1,589,752 individuals (1,025,232 men and 564,520 women) had been diagnosed with GC at least 5 years earlier, yielding a worldwide prevalence of 20.8 per 100,000 (26.6 in men and 14.9 in women).

## 1.2 Risk Assessment and Stratification in Gastric Cancer

Most GC cases (about 90%) are sporadic, while only 10% show a familial aggregation, and 1–3% arise from inherited cancer syndromes [5]. Hence most GC cases arise from the interplay of genetic and environmental factors, whose weight increases with aging. An important contribution to GC decline has been given by identifying relevant risk factors, which can be classified into two general groups: environmental and host-related factors.

The majority of GC cases are related to chronic infection with *Helicobacter pylori*, which is the strongest known environmental risk factor for GC, accounting for 89% of cases worldwide [6]. Indeed, de Martel et al. estimated that, in 2018, 760,000 cases of non-cardia cancer could be attributed to *H. pylori* infection, as well as 36,000 cases of cardia cancer and 16,000 of gastric non-Hodgkin lymphoma [7]. *H. pylori* was classified by the World Health Organization (WHO) as a class I carcinogen in the early 1990s, and this recently confirmed by the International Agency for Research on Cancer (IARC) [8, 9]. The cytotoxin-associated gene A (cagA) increases the virulence of *H. pylori*: compared with non-infected individuals, the odds ratio (OR) of GC is 2.31 (95% CI 1.58–3.39) in people with *H. pylori*

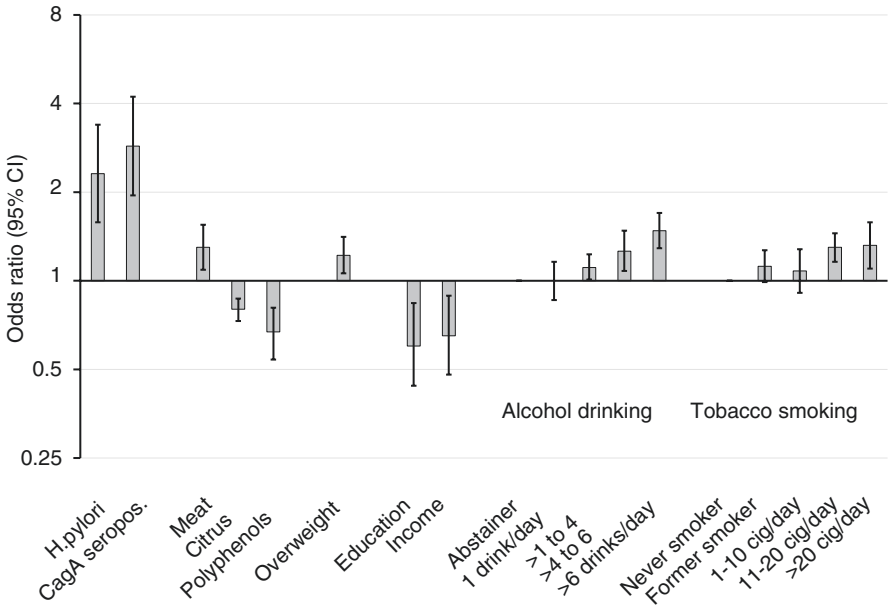


**Fig. 1.1** Main risk factors for gastric cancer. Sources of risk estimates: *H. pylori* infection and CagA seropositivity [10]; highest vs. lowest tertile of meat [13] and citrus [14] consumption; highest vs. lowest quartile of polyphenol intake [18]; overweight/obesity vs. normal weight [19]; highest vs. lowest level of education [20]; highest vs. lowest household income [20]; alcohol drinking [22]; tobacco smoking [25]

infection, and increases to 2.87 (1.95–4.22) in people with cagA seropositivity [10]. Generally, the natural history of *H. pylori*–related GC includes a latency period, followed by a preclinical stage, where the risk increases exponentially [11]. Although *H. pylori* eradication involves healing from gastric mucosa inflammation, eradication alone cannot immediately reverse the "peak" risk, but it does place the individual on a more favorable trajectory [12].

Substantial evidence suggests that diet has an important role in the onset of GC (Fig. 1.1). In detail, the risk is increased by a high intake of meat [13] and salty or smoked food, and decreased by a diet rich in fresh fruit and vegetables [14]. Salt can directly damage the stomach mucosa [15] and increase the persistency of *H. pylor*i infection in animal models [16]. The protective effect of fresh fruit and vegetables can be attributed to the high content of antioxidants, such as ascorbic acid, carotenoids and polyphenols [17, 18].

Excess body weight is associated with a slight increase in the risk of GC: according to a meta-analysis of cohort studies, the OR of GC is 1.22 (95% CI 1.06–1.41) in overweight/obese compared with normal weight subjects [19]. Of note, the association was stronger for cardia (OR = 1.55, 1.31–1.84) than for non-cardia (OR = 1.18, 0.96–1.45) GC.

GC risk is inversely related to socioeconomic status, e.g., education level and household income. In a recent meta-analysis, the pooled OR for the highest compared to the lowest level of education was 0.60 (95% CI 0.44–0.84). The negative association was recorded both for non-cardia (OR 0.39, 95% CI 0.22–0.70) and cardia (OR 0.47, 95% CI 0.22–0.99) GC [20].

Alcohol drinking is a major risk factor for esophageal cancer, but plays a minor role also in gastric oncogenesis. In a nationwide South Korean cohort study [21], the hazard ratio (HR) showed a risk for esophageal cancer three times higher in people drinking ≥30 g alcohol/day than non-drinkers (HR = 3.13, 95% CI 2.95–3.32), while the risk for GC was increased by only one-fourth (HR = 1.24, 1.21–1.26). A similar result was found by a cohort study from the Stomach cancer Pooling (StoP) project [22], where the pooled OR for GC, compared to abstainers, was 1.26 (95% CI 1.08–1.48) in people consuming >4–6 drinks per day and 1.48 (1.29–1.70) in people consuming >6 drinks/day. It is still debated whether moderate alcohol consumption (<10 g/day) does not affect [22] or slightly increases [21] GC risk. The carcinogenic effect of alcohol seems to be higher for gastric cardia (OR for heavy drinkers = 1.61, 95% CI 1.11–2.34) than non-cardia (OR = 1.28, 95% CI 1.13–1.45) cancer [22].

Tobacco smoke is one of the most important risk factors for cancer. For instance, cigarette smokers are 15–30 times more likely to develop lung cancer than non-smokers [23]. Tobacco smoke has a significant, although lesser, effect also on the stomach mucosa [24]. According to the StoP project, compared to never smokers, the ORs of GC were 1.12 (95% CI 0.99–1.27) for former smokers, and 1.25 (95% CI 1.11–1.40) for current cigarette smokers. The ORs were slightly higher for cardia (1.58, 95% CI 1.11–2.24) than non-cardia (1.29, 95% CI 1.03–1.61) cancer [25].

Infection with Epstein-Barr virus (EBV) is associated with GC especially in men and is characterized by DNA-methylation of specific regions of different cancer-associated genes.

As regards cancer site and histology, obesity and alcohol drinking have a larger impact on cardia than non-cardia cancer (Fig. 1.2), while alcohol drinking and tobacco smoke tend to have a larger effect on the onset of intestinal compared with diffuse histotypes (Fig. 1.3). Indeed, the latter histotype seems to be more affected by genetic factors and less affected by environmental factors compared with the intestinal histotype.

## 1.3 Prevention

There are two main strategies for preventing cancer: (1) primary prevention consists in removing cancer causes before cancer occurrence; (2) secondary prevention consists in early cancer detection through mass screening.

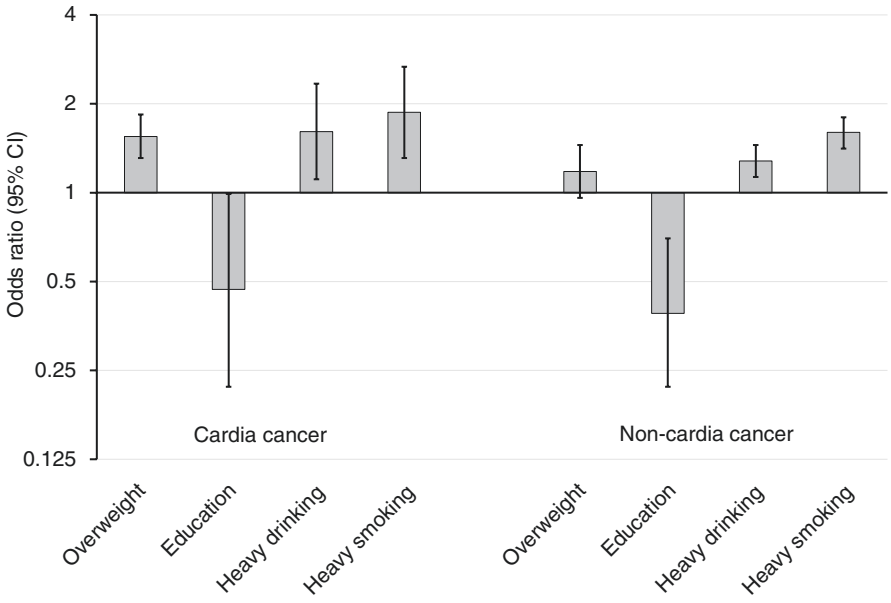


**Fig. 1.2** Risk factors for gastric cancer as a function of tumor site (cardia vs. non-cardia cancer). Sources of risk estimates: overweight/obesity vs. normal weight [19]; highest vs. lowest level of education [20]; heavy alcohol drinking (4–6 drinks/day) vs. abstainer [22]; heavy tobacco smoking (>20 cigarettes/day) vs. never smoking [25]

### 1.3.1 Primary Prevention

As regards GC, primary prevention can be accomplished by avoidance of known carcinogens, changes in lifestyle, inhibiting cancer development through prescription of anti-carcinogenic drugs [26], and, above all, eradicating *H. pylori*.

Nonsteroidal anti-inflammatory drugs (NSAIDs), statins, and metformin seem to have a protective effect on GC [27]. Aspirin and NSAIDs inhibit cell proliferation and induce apoptosis in various cancer cell lines. The protective effect of aspirin (RR 0.70, 95% CI = 0.62–0.80) seems to be slightly higher than that of NSAIDs (RR 0.86, 95% CI = 0.80–0.94) [28]. Statins have been reported to reduce GC risk by 15–20% [29].

*H. pylori* eradication halves the incidence of GC both in healthy individuals (RR = 0.54, 95% CI 0.40–0.72, NNT = 72) and in survivors of previous GC (RR = 0.49, 95% CI 0.34–0.70, NNT = 21) and reduces, as a consequence of the lower incidence, also mortality from GC, although to a lower extent (RR = 0.61, 95% CI 0.40–0.92, NNT = 135) [30]. The Taipei Global Consensus, released by the Asian Pacific Alliance on Helicobacter and Microbiota, pointed out that "the

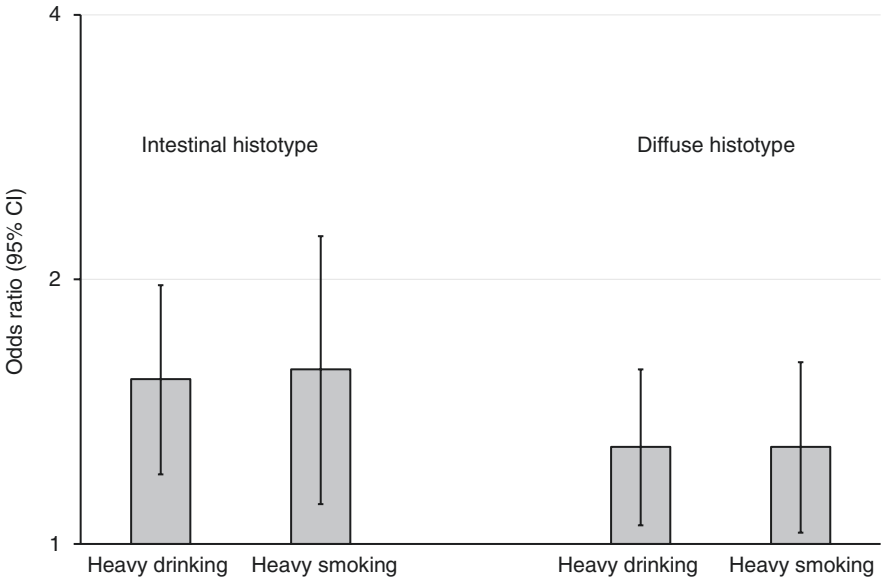


**Fig. 1.3** Risk factors for gastric cancer as a function of Laurén histology (intestinal vs. diffuse histotype). Sources of risk estimates: heavy alcohol drinking (4–6 drinks/day) vs. abstainer [22]; heavy tobacco smoking (>20 cigarettes/day) vs. never smoking [25]

strategy of screen-and-treat for *H. pylori* infection is most cost-effective in young adults in regions with a high incidence of GC and is recommended preferably before the development of atrophic gastritis and intestinal metaplasia. However, such a strategy may still be effective in people aged over 50, and may be integrated or included into national healthcare priorities" [31].

### 1.3.2 Secondary Prevention (Screening)

Cancer diagnosis is often delayed as a substantial proportion of patients are either asymptomatic or, more commonly, have non-specific symptoms during the early stage of the disease. The purpose of cancer screening is to reduce cancer mortality and, for some cancers, also morbidity, by detecting early preclinical disease, which can be effectively treated unlike advanced cancer. In order to be advantageous, a screening program should be well-organized and ensure high coverage of the population at risk. To achieve these goals, a screening test should be accurate, feasible, culturally acceptable, safe, and low cost. To minimize the possible harms and increase the expected benefits of a screening program, diagnostic tests should be evidence-based, quality-assured, and equitably distributed [32].

Secondary prevention is currently ongoing in eastern Asia, which presents the highest incidence in the world [33]. In Japan, screening was introduced in the sixties, first restricted to the population older than 50 years and later extended to all

people aged 40 years and over, and it is based on double-contrast barium radiograph with photofluorography [34, 35]. At present, the Japanese guidelines recommend radiographic or endoscopic screening for people aged 50 years and over [34], while the Korean guidelines recommend endoscopy every 2 years for people aged >40 years [36].

On the other hand, no organized screening program can be found outside Japan and South Korea, although several screening approaches have been proposed. In the West, proposed GC screening programs are mainly focused on people with premalignant lesions, such as atrophy or *H. pylori* infection/inflammation, and employ upper endoscopy and double-contrast barium radiography with photofluorography or digital radiography. Among the two techniques, upper endoscopy is the most sensitive in diagnosing a variety of gastric lesions, but also the most expensive and the most invasive.

Non-invasive screening approaches have also been proposed which assess the blood concentration of specific markers, in particular pepsinogen and gastrin-17b. Pepsinogen levels decrease in atrophic gastritis, while gastrin-17b decreases in atrophic gastritis affecting the antrum or the whole stomach, while an opposite trend is recorded for atrophic gastritis in the body/fundus. However, the interpretation of these biomarkers is not straightforward, as pepsinogen levels increase during inflammation, while gastrin-17b levels decrease in gastroesophageal reflux disease and increase during treatment with proton-pump inhibitors. In Europe, a two-step screening has been proposed: first, subjects at high risk for GC are identified through a set of biomarkers, named Gastropanel (International Institute of Anticancer Research. Delinasios GJ) and comprising pepsinogen I, pepsinogen II, gastrin-17b and IgG to *H. pylori* [37]. In the second step, high-risk subjects are referred for gastroscopy. However, the implementation of this two-step strategy has been limited by the relatively high cost of biomarker assessment, which is amplified by its allocation in first-line screening.

It should be pointed out that a screen of the general European population is not feasible, unless a careful selection of at-risk categories is preliminarily performed. For instance, if the European population aged 55–69 years were screened every 2 years, the proportion of new cases would be 53.6/100,000 person-years × 2 years = 0.107% in men and 21.8/100,000 person-years × 2 years = 0.044% in women. Even assuming a fairly high sensitivity and specificity of 0.95, the positive predictive value would be 1.95% in men and 0.83% in women. In other words, only two men and less than one woman out of 100 individuals positive to the initial screen and referred for further examinations would be finally diagnosed with GC.

## 1.4 Discussion

Screening has been proved to be a lifesaving procedure in several tumors, including breast, endometrial and colorectal cancers. However, the risk-benefit balance is less favorable for other cancers, such as prostate or lung cancer.

To be cost-effective, a screening program should achieve an adequate positive predictive value (PPV). For instance, PPV is around 8% in breast cancer screening [38], and should not be lower than that to avoid increases in psychological and physical stress for the patients and costs for the health system. Screening programs, based on imaging or gastroscopy, have proved effective in anticipating GC diagnosis and reducing related mortality in South Korea and Japan, which have the highest incidence in the world [27]. However, at present a hypothetical screening on the European population aged 55–69 years would achieve a PPV <2% in men and <1% in women, due to the relatively low incidence of GC. To enhance PPV, a two-step approach should be adopted, where high-risk individuals should be detected in the first step through the use of simple tools, such as questionnaires or cheap non-invasive tests, and then referred for invasive procedures.

However, only weak risk factors emerged during the present review, as denoted by ORs comprised between 1 and 1.5, with the only exception of *H. pylori* infection, whose detection is rather expensive to be applied to the general population. Screening based on the blood concentration of specific biomarkers, such as the Gastropanel, is not feasible as a first-step screen for the same reason.

It should be remembered that even cost-effective approaches cannot be implemented in several regions due to resource constraints. Hence, an integrated and resource-sensitive approach should be developed for real-life practice [39].

## 1.5 Conclusion

In the West, there is no standard approach to GC screening. Endoscopic screening appears to be a viable option for high-risk areas, while serological screening can be used to identify high-risk individuals to be referred for endoscopic surveillance.

A strategy that combines adequate risk stratification with gastroscopy on pre-selected individuals could lead to an increase in early diagnosis and hopefully in patient survival and quality of life, as well as gastric pre-cancer surveillance. A future approach worth exploring would be to select high-risk individuals from healthcare utilization databases, routinely analyzed through innovative approaches, such as artificial intelligence [40].

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# 2 Molecular Classification of Gastric Cancer: A New Perspective for Therapy and Prognosis?

Simona Corso and Silvia Giordano

The Cancer Genome Atlas (TCGA) and the Asian Cancer Research Group (ACRG), independently, reported two gastric cancer whole-genome molecular profiles, proposing two molecular classifications for gastric adenocarcinomas [1, 2].

## 2.1 The TCGA Molecular Classification

TCGA analyzed 295 primary gastric adenocarcinomas integrating distinct "omics" platforms that allowed the classification into four molecular subtypes (Fig. 2.1):

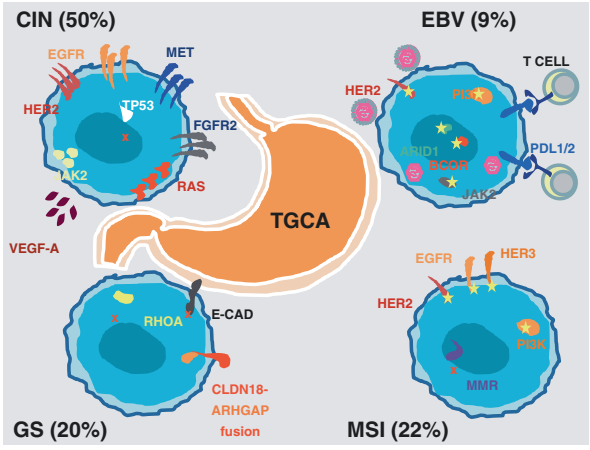


**Fig. 2.1** Schematic representation of the most frequent genetic alterations identified in the subgroups defined by The Cancer Genome Atlas (TCGA). Details are given in the text

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- **EBV (Epstein-Barr virus)-positive tumors**
  Epstein-Barr virus (EBV) is found in around 9% of gastric cancers, more frequently located in the gastric fundus or body (62%). EBV+ tumors show a higher prevalence of DNA hypermethylation than any other cancers, displaying an extreme CIMP (CpG island methylator phenotype), including *CDKN2A* promoter hypermethylation, but lacking MLH1 hypermethylation, characteristic of microsatellite instability (MSI)-associated CIMP. Moreover EBV+ tumors also display a strong incidence of *PIK3CA* mutations (80% vs. 3–20% in the other subgroups), quite dispersed along the gene sequence. Other frequently mutated genes are *ARID1A* (55%) and *BCOR* (23%) while *TP53* is only rarely mutated. Amplification at the 9p24.1 locus containing genes encoding for *JAK2*, *PD-L1* and *PD-L2* genes is quite frequently observed, suggesting that targeting of the JAK kinase and the use of checkpoint inhibitors should be tested in this tumor subgroup.
- **CIN (chromosomal instability) tumors**
  This subgroup includes around 50% of gastric adenocarcinomas, frequently located at the gastroesophageal junction/cardia (65%). These tumors show the highest frequency of p53 mutation (71%), marked aneuploidy and focal amplification of receptor tyrosine kinases. Amplification of *EGFR* (10%), *HER2* (24%), *HER3* (8%), *JAK2* (5%), *FGFR2* (8%), *MET* (8%), *PIK3CA* (10%) and *NRAS/KRAS* (18%) are frequent.
- **GS (genomically stable) tumors**
  This subgroup includes around 20% of gastric adenocarcinomas. They often present diffuse type histology and alterations in genes involved in cell adhesion such as *RHOA*, *CDH1* and *CLDN18/ARHGAP26* and elevated expression of angiogenesis-related pathways. Somatic mutations of *CDH1* (encoding for cadherin, a protein involved in cell-to-cell adhesion) are found in around 37% of cases (germline mutations of this gene are responsible for hereditary diffuse GC). Mutations of *RHOA*, a protein controlling actomyosin-dependent cell motility, are present in 15% of GS. Other proteins involved in cell adhesion/motility frequently altered in GS are *CLDN18* (encoding for a component of tight junctions) and *ARHGAP26* (a GTPase-activating protein that facilitates RHOA inactivation). Alterations of *RHOA*, *CLDN18* and *ARHGAP26* are mutually exclusive and altogether affect 30% of GS. As these alterations likely result in activation of the RHOA-dependent pathway, they can contribute to the invasive behavior of diffuse GC. Recently, it was demonstrated that *RHOA* somatic mutations are more frequent in late-onset diffuse GC compared to early-onset tumors [3] and that *RHOAY42C*, the most common *RHOA* mutation in diffuse GC, is oncogenic and pro-metastatic [4].
- **MSI (microsatellite instability) tumors**
  This subgroup includes around 22% of gastric adenocarcinomas. MSI tumors display elevated mutation rates and hypermethylation. Mutations of kinases such as *EGFR*, *HER2*, *HER3*, *JAK2*, *FGFR2*, *MET* and *PIK3CA* are present. Moreover, alterations in the major histocompatibility complex class I genes are common and likely lead to loss of expression of the HLA class I complex, reducing antigen presentation to the immune system.

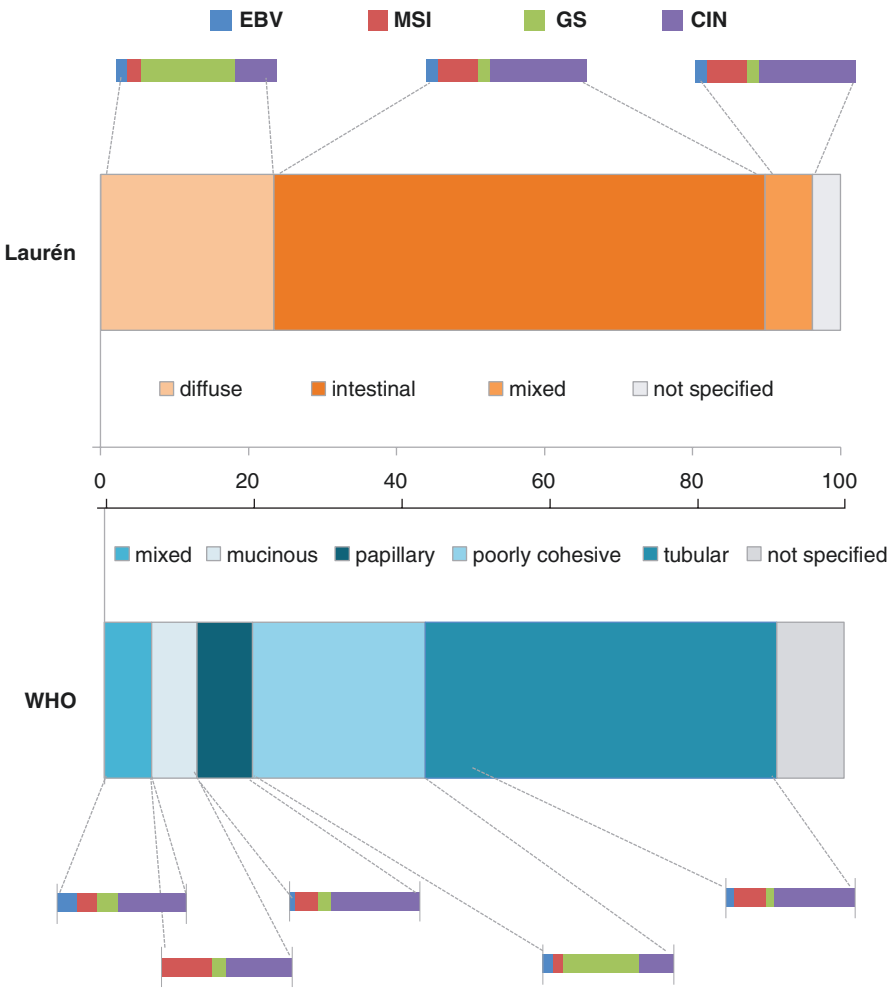


**Fig. 2.2** Distribution of the histological types (according to Laurén, upper part, and WHO, lower part) in the subgroups identified by The Cancer Genome Atlas (TCGA)

As discussed, there is no clear correlation between the identified molecular subtypes and the classical pathologic classifications (Fig. 2.2). The main relevance of the TCGA classification stems from the identification, in the different subgroups, of possible therapeutic targets. Indeed, EBV+ tumors are endowed with a high frequency of mutated *PIK3CA*, which is a targetable gene. Both EBV+ (showing *PDL1/2* amplification and overexpression) and MSI tumors (displaying a high mutational board) are likely candidates for immunotherapy. Several therapeutic targets are found in CIN tumors (which represent around half of all GCs) where different receptor tyrosine kinases (RTKs) are found amplified and are likely drivers in these tumors. Clinical trials are in fact ongoing to define if and how their targeting is effective. Finally, for the GS subtype, even if potential targets have been identified, none of them is, at present, targetable.

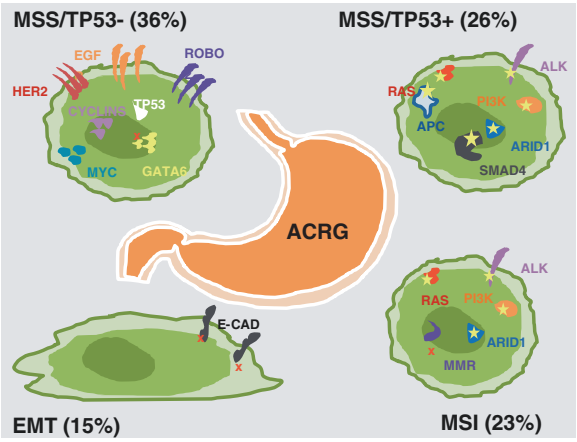


**Fig. 2.3** Schematic representation of the most frequent genetic alterations identified in the subgroups defined by the Asian Cancer Research Group (ACRG). Details are given in the text

## 2.2 The ACRG Molecular Classification

A second classification has been proposed by the ACRG [2]. The authors analyzed 300 tumors and identified four subtypes (Fig. 2.3).

- **MSI**
  The MSI subtype occurs mainly in the antrum (75%), shows preferentially an intestinal subtype (>60%), is mostly diagnosed at early stages (I–II), and shows the best prognosis. Liver-limited metastases are more frequent in this subtype. The MSI subtype is associated with the presence of hypermutations in genes such as *KRAS* (23%), *ALK* (16.3%), *ARID1A* (44.2%), and those involved in the PI3K pathway (42%). It shows MLH2 loss of RNA expression and an elevated DNA methylation signature.
- **MSS/EMT**
  The MSS/EMT subtype occurs at a younger age, is mainly of the diffuse type, is diagnosed at late stages, and shows the worst prognosis. Moreover, the MSS/EMT type is associated with a higher chance of recurrence compared with MSI (63% versus 23%), with a high frequency of peritoneal seeding. The MSS/EMT subtype presents loss of epithelial markers, *CDH1* loss and a lower mutation frequency compared with the other MSS groups.
- **MSS/TP53+**
  The MSS/TP53+ subtype presents a higher frequency of mutations in *APC*, *ARID1A*, *KRAS*, *PIK3CA*, and *SMAD4*. EBV positivity occurs more frequently than in other subtypes; EBV+ tumors are enriched in *PIK3CA* and *ARID1A* mutations. The MSS/TP53+ subtype shows an intermediate prognosis and chance of recurrence. It is found more frequently in the body of the stomach.
- **MSS/TP53−**
  The MSS/TP53− subtype exhibits the highest prevalence of TP53 mutations (60%). Genomic instability is present in 28% of all cases and it is significantly

associated with the MSS/TP53− subtype. Like MSS/TP53+ it has an intermediate prognosis and chance of recurrence. It shows *TP53* mutations and amplification of genes such as *HER2*, *EGFR*, *CCNE1*, *CCND1*, *MDM2*, *ROBO2*, *GATA6*, *MYC*. This type has the highest frequency of lymphovascular invasion.

The ACRG analysis also found that the first site of recurrence differs according to the subtype: peritoneal seeding is more frequent in the MSS/EMT (64% versus 23%), while liver-limited metastases are more frequent in the MSI (23%) and MSS/TP53− subtypes (21%). *Helicobacter pylori* infection was found in 42.5% of cases but no correlation with the subtypes was observed.

## 2.3 Stroma-Based Molecular Classifications

Some groups have also analyzed the contribution of the stroma in impacting gastric cancer prognosis. The group led by Tan analyzed intratumoral stroma as a predictor of survival in patients with gastric cancer [5]. In primary GC the authors identified 178 expression modules which were associated with biological processes, chromosomal location patterns and clinicopathological parameters. Expression of the stromal module was associated with significantly poorer overall survival. High stromal expression was also correlated with the histologic type, being higher in diffuse than in intestinal tumors; in this case as well, a correlation with survival was observed. Finally, a significant positive correlation was found between the expression of the stromal module and the morphometric quantification of intratumoral stroma. A Kaplan-Meier analysis revealed that patients with high intratumoral stroma had a poorer prognosis.

Benjamin's group [6] further investigated stromal-based signatures in order to identify features suggesting response to stroma-directed therapies. They identified four primary stromal phenotypes, namely: (1) vascular immature/non-inflammatory (rudimentary vessels in an immature stroma, no significant lymphocyte infiltration); (2) inflammatory (immature angiogenic markers and high levels of lymphocytes); (3) vascular mature/inflammatory; (4) vascular mature. Their findings suggest that a tumor stroma-based genomic classification could help the identification of predictive biomarkers of response to antiangiogenetic agents and/or immunotherapy, thus improving patient stratification.

## 2.4 Comparison of the Molecular Classifications

Both the TCGA and ACRG classifications have potential clinical implications for gastric cancer treatment even if they show differences. An MSI subtype characterized by a high mutation frequency was identified in both classifications, even though its prognostic value was observed only by the ACRG group (whose follow-up is significantly longer), while TCGA GS, EBV+, and CIN subtypes were enriched in ACRG MSS/EMT, MSS/TP53+, and TP53−, respectively. It is not easy to explain

why these two classifications are only partially overlapping. Possibilities are: the analysis of tumors differing in histotype and anatomic site, the ethnic origin of the patients (mainly from Korea in the ACRG and from the USA and Western Europe in the TCGA) or the use of different technological platforms.

Nevertheless, these two molecular classifications represent an important step forward in improving our knowledge of the molecular basis of GC as they provide a roadmap for patient stratification and the design of clinical trials. Concerning molecular therapies, only one agent targeting cancer cells has been approved so far for advanced GC by the FDA and the European Union, namely the HER2 monoclonal antibody trastuzumab in HER2-amplified tumors. However, these molecular analyses have shown that other druggable targets are present in the different subgroups and should be tested in molecularly selected patients.

The stroma-based molecular classification, instead, could help identify tumors which are likely to respond to antiangiogenic therapy as well as to immunotherapy. Indeed, the anti-vascular endothelial growth factor receptor 2 (VEGFR-2) mAb ramucirumab has shown clinical activity both as monotherapy and in combination with paclitaxel for patients with gastric cancer who have progressed after first-line chemotherapy; however, as yet there is no biomarker to identify responding patients.

The anti-PD-1 antibodies nivolumab and pembrolizumab were licensed in Japan and the USA, respectively, for patients with heavily treated, chemo-resistant GC/gastroesophageal junction cancer; more recently, nivolumab also gained approval in China. However, the immune checkpoint inhibitors (ICI) provided only modest survival benefit, likely in subgroups with MSI-high, EBV+ or high mutation burden [7]. There is thus an urgent need for the identification of accurate biomarkers that can predict the response to immunotherapy, as well as the development of combinatorial approaches to maximize the efficacy of ICI.

## 2.5 Conclusions

The described molecular analyses have increased our knowledge of gastric cancer biology; however, the clinical impact of these classifications on prognosis and response to therapy is, at present, only seen for the MSI and the EBV+ subtypes [8–11]. This has led several centers to test the MSI status to guide clinical decisions. Unfortunately, this does not hold true for the other subtypes, where molecular analysis does not impact therapeutic choices, apart from HER2 evaluation to consider trastuzumab treatment.

It is thus necessary that the improved molecular knowledge stemming from "omic" technologies be considered as a milestone to significantly ameliorate the efficacy of GC treatment.

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# Histological Classifications of Gastric Tumors: Toward a Global Harmonization

3

Luca Saragoni, Serena Battista, Maria Raffaella Ambrosio, and Anna Tomezzoli

## 3.1 Introduction

There are two different perspectives between Eastern and Western physicians on many aspects of the diagnosis and treatment of gastric cancer. These discrepancies have historical bases, but they persist to this day where the opportunities to share data and experiences in order to reach global consensus have greatly increased compared to the past.

From the pathological point of view, there are two main differences between the East and the West:

- Diagnostic criteria used to discriminate between high-grade intra-epithelial neoplasia/dysplasia and invasive carcinoma.
- Classifications used to identify morphologically different subtypes of gastric carcinoma.

Harmonization of these two issues is desirable in order to provide strong evidence that would be applicable worldwide.

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## 3.2 Histological Diagnostic Criteria

Intra-epithelial neoplasia of the stomach represented an important diagnostic challenge due to the existence in the past of different criteria between Western and Eastern countries. The differential diagnosis between intra-epithelial neoplasia/dysplasia and carcinoma was simply made on the basis of cytological and architectural atypia by Japanese pathologists, while Western colleagues considered the invasion of the mucosal layer to be mandatory for an appropriate diagnosis of carcinoma.

Features of cytological abnormality included variation in nuclear size and shape; presence of hyperchromatic large, spherical, vesicular nuclei; irregular clumped chromatin; increased frequency of mitotic figures; pseudostratified nuclei; poor cellular differentiation, increased nuclear/cytoplasmic ratio, and loss of nuclear polarity.

Features of architectural abnormality included increased crypt complexity with crowding, branching glandular epithelium, fused glands, budding, a cribriform pattern of growth and variability of crypt size and shape. According to these criteria, the Japanese classification of gastric epithelial lesions in 1998 [1] included the following categories:

| | |
|---|---|
| *Group I* | Normal or benign |
| *Group II* | Benign with atypia |
| *Group III* | Borderline lesions |
| *Group IV* | Strongly suspicious for invasive carcinoma |
| *Group V* | Definitive for invasive carcinoma |

However, Western pathologists considered only lesions with invasion of the mucosal layer to be carcinomas; the criteria of infiltration were first precisely defined in the 2010 WHO Classification [2]. In particular, desmoplastic changes, single infiltrating cells in the lamina propria, marked glandular crowding, excessive branching, budding and intraluminal necrotic debris were identified as signs of invasion. The 2010 WHO classification considered intra-epithelial neoplasia and dysplasia as synonyms, identifying the following categories (Figs. 3.1 and 3.2):

1. Negative for intra-epithelial neoplasia/dysplasia
2. Indefinite for intra-epithelial neoplasia/dysplasia
3. Low-grade intra-epithelial neoplasia/dysplasia
4. High-grade intra-epithelial neoplasia/dysplasia
5. Intramucosal invasive neoplasia/intramucosal carcinoma

Moreover, the use of the term “carcinoma in situ” for columnar precursor lesions of high grade was strongly discouraged.

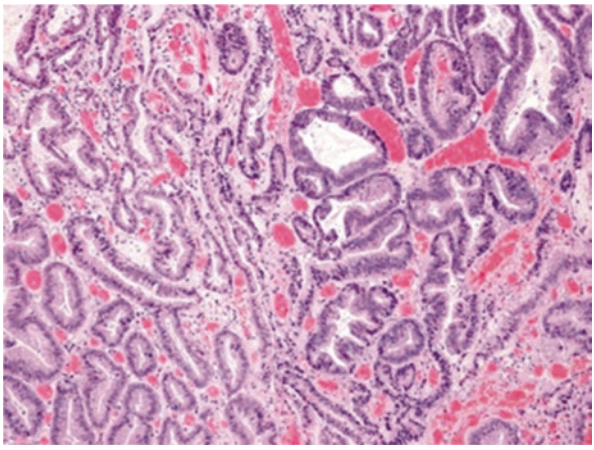

**Fig. 3.1** Low-grade (*left*) and high-grade (*right*) gastric dysplasia

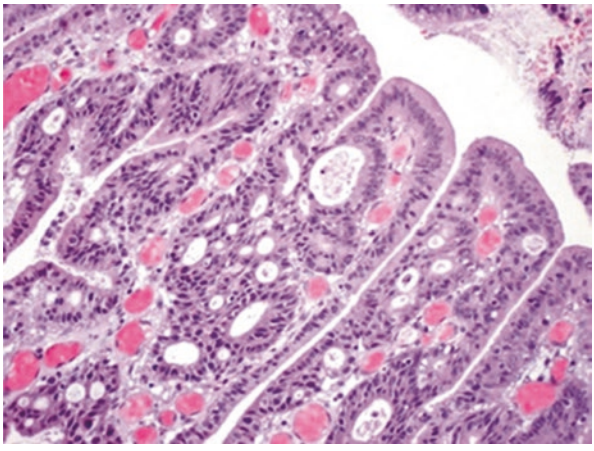

**Fig. 3.2** Intramucosal gastric carcinoma

## 3.3 Attempts to Provide Standardization of Diagnosis

Two important steps were made in order to provide the standardization of diagnosis of gastric carcinoma between the East and West. First in 1998, Western and Eastern pathologists, chosen among the most expert in the field of gastrointestinal tumors, conceived the Vienna Classification of Gastrointestinal Epithelial Neoplasia [3]. This classification was meant to be applied throughout the entire gastrointestinal tract and used for both bioptic and resected material. The main advantage of this system was represented by recommending a precise clinical behavior to the clinicians for each category, especially when the diagnosis was made on biopsy (Table 3.1).

This classification was practical, but the fact that it was applied to the whole gastrointestinal tract represented its most important drawback. Moreover, despite Japanese and Western pathologists sharing the sub-categorization of gastrointestinal

**Table 3.1** Recommendations based on the categories of the Vienna classification

| Category | Clinical recommendation |
|---|---|
| 1. Negative for neoplasia | Optional surveillance |
| 2. Indefinite for neoplasia | Surveillance/Repeat biopsy |
| 3. Noninvasive low-grade dysplasia | Surveillance/Local treatment |
| 4. Noninvasive high-grade dysplasia | Local treatment |
| 5. Invasive carcinoma | Local/Surgical treatment |

epithelial tumors defined in the Vienna Classification, the diagnostic criteria they used continued to be different.

In detail, unlike Western pathologists, the Japanese do not need to directly detect the invasion of the lamina propria in order to define a lesion as "suspected for invasive carcinoma".

For this reason, in 2003 Stolte introduced the revised Vienna classification [4]. He entered intramucosal carcinoma into category 4 of "non-invasive high-grade neoplasia". The Padova classification was another attempt to reach a consensus between the East and the West [5], with the introduction of category 3.2.1 "suspicious for invasive carcinoma". Table 3.2 shows the comparison between the different classifications.

However, until now the underlying difference, which is the adoption of cytoarchitectural criteria by the Japanese and the anatomic criteria of invasion by the Western pathologists, should be made explicit and harmonized. This would homogenize the diagnosis on gastric biopsies in those cases in which invasion of the lamina propria is strongly suspected but not directly seen.

## 3.4 Histological Classifications of Gastric Cancer Subtypes

One of the specific features of gastric cancer is its well-known morphological heterogeneity, which has led to the development of many classifications, both in the East and West, aiming to categorize its different morphological subtypes.

The most used are the Laurén, the Japanese and the WHO classifications [6–8]. Japanese and Korean pathologists also used the Nakamura classification, which simply distinguishes differentiated from undifferentiated tumors. As shown in Table 3.3**,** Western pathologists used to discriminate gastric cancer cases in intestinal, diffuse and mixed tumors according to Laurén. If the WHO classification is used, the papillary, tubular, mucinous, poorly cohesive (including the signet ring cell type) and mixed types could be identified.

A substantial correspondence between these two classifications widely adopted in the West is possible as the tubular, papillary and mucinous categories overlap with the Laurén intestinal type, while the class of poorly cohesive/signet ring cell tumors corresponds to the Laurén diffuse type.

The problem arises when attempting to find a clear correspondence between the Laurén/WHO and the Japanese classifications [8]. Indeed, the Japanese classification identified several subtypes: papillary, well-differentiated tubular, signet ring

**Table 3.2** Comparison between the different classifications of gastric epithelial dysplasia

| Japanese (1998) | Western (1998) | Padova (1998) | | Vienna (1998) | | | WHO (2000 and 2010) |
|---|---|---|---|---|---|---|---|
| Group I: Normal or benign | Negative for dysplasia | Category 1: Negative for dysplasia | | Category 1: Negative for dysplasia | | | No intraepithelial neoplasia/ dysplasia |
| Group II: Benign with atypia | Indefinite for dysplasia | Category 2: Indefinite for dysplasia | | Category 2: Indefinite for dysplasia | | | Indefinite for intraepithelial neoplasia/dysplasia |
| Group III: Borderline | Low-grade adenoma | Category 3.1: Non-invasive low-grade neoplasia (low-grade adenoma/dysplasia) | | Category 3: Non-invasive low-grade neoplasia (low-grade adenoma/dysplasia) | | | Low-grade intraepithelial neoplasia/dysplasia (low-grade adenoma; low-grade dysplasia) |
| | Low-grade dysplasia | | | | | | |
| Group IV: Strongly suspicious for invasive carcinoma | High-grade adenoma | Category 3.2: Non-invasive high-grade neoplasia (high-grade adenoma/dysplasia) | | Category 4: Non-invasive high-grade neoplasia | | | High-grade intraepithelial neoplasia/dysplasia (high-grade adenoma; high-grade dysplasia) |
| | High-grade dysplasia | Category 3.2.1: Suspicious for carcinoma (without lamina propria invasion) | Category 3.2.2: Non-invasive carcinoma (CIS) | Category 4.1: High-grade adenoma/ dysplasia | Category 4.2: Non-invasive mucosal carcinoma | Category 4.3: Suspicious for invasive carcinoma | |
| Group V: Definitive invasive carcinoma | Invasive carcinoma | Category 4: Suspicious for invasive carcinoma (with lamina propria invasion) | | Category 5: Invasive neoplasia | | | Intramucosal invasive neoplasia (intramucosal invasive carcinoma) |
| | | Category 5: Invasive neoplasia (intramucosal/ submucosal carcinoma or beyond) | | Category 5.1: Intramucosal carcinoma | Category 5.2: Submucosal carcinoma or beyond | | Invasive neoplasia |

**Table 3.3** Comparison between the different histological classifications of gastric cancer

| Laurén (1965) | Nakamura (1968) | JGCA (2017) | | WHO (2019) |
|---|---|---|---|---|
| Intestinal | Differentiated | Papillary: pap<br>Tubular 1, well-differentiated: tub 1<br>Tubular 2, moderately differentiated: tub 2 | | Papillary<br>Tubular, well-differentiated<br>Tubular, moderately differentiated |
| | | Poorly differentiated | Solid type (por 1) | Tubular, poorly differentiated (solid) |
| Indeterminate | Undifferentiated | | Non-solid type (por 2) | Poorly cohesive (PC) including SRC:<br>– Pure SRC: SRC1 (>90%)<br>– PC with SRC component: SRC2 (10–90%)<br>– PC-NOS: SRC3 (<10%) |
| Diffuse | Undifferentiated | Signet ring cell carcinoma (SRC): sig | | |
| Intestinal/diffuse/ determinate | Differentiated/ Undifferentiated | Mucinous | | Mucinous |
| Mixed | | Description according to the proportion (e.g., por2 > sig > tub2) | | Mixed |
| Not defined | Not defined | Special type:<br>– Adenosquamous carcinoma<br>– Squamous cell carcinoma<br>– Undifferentiated carcinoma<br>– Carcinoma with lymphoid stroma<br>– Hepatoid adenocarcinoma<br>– Adenocarcinoma with enteroblastic differentiation<br>– Adenocarcinoma or fundic gland type | | Histological variants:<br>– Adenosquamous carcinoma<br>– Squamous cell carcinoma<br>– Undifferentiated carcinoma<br>– Carcinoma with lymphoid stroma<br>– Hepatoid carcinoma<br>– Adenocarcinoma with enteroblastic differentiation<br>– Adenocarcinoma of fundic gland type<br>– Micropapillary adenocarcinoma |

*JGCA* Japanese Gastric Cancer Association, *NOS* not otherwise specified

cell and poorly differentiated tumors. Of note, this latter category of poorly differentiated tumors contains both the poorly differentiated tubular cases (which are the poorly differentiated solid type: por1) corresponding to Laurén intestinal tumors, and the poorly differentiated non-solid type which corresponds to Laurén diffuse types.

As a result, when Japanese authors perform studies and draw conclusions on poorly differentiated tumors, we should be aware that some intestinal and diffuse types have been considered together.

In order to solve this problem, the European chapter of the International Gastric Cancer Association suggested the adoption of the WHO classification for each newly diagnosed gastric cancer [9].

Specifically, the recent fifth edition of the WHO classification [10] should be used. This also allows a better definition of the histological subgroup of poorly cohesive carcinoma, which has been subdivided into three categories according to the amount of tumor cells displaying the features of signet ring cells [9] (Table 3.3).

Addressing these discrepancies and globally harmonizing the terms used to define the different morphological subtypes of gastric cancer are crucial steps toward the proper comparison of data and experiences between the East and the West.

In conclusion, in order to definitely improve the quality of research in the field of gastric cancer, we should rely on Eastern and Western thinkers:

> *Tzu-lu said: "If the Lord of Wei left the administration of his state to you, what would you put first?". The Master said, "If something has to be put first, it is perhaps the rectification of names." (Analects, XIII, 3, translated by D.C. Lau).*
>
> *"The most valuable of all talents is that of never using two words when one will do." (Thomas Jefferson).*

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# The New Field of View of Endoscopy and Histological Diagnosis

4

Filippo Catalano, Antonello Trecca, Raffaele Borghini, and Simone Giacopuzzi

## 4.1 Introduction

In Western countries the role of upper gastrointestinal endoscopy (UGE) has been limited to the investigation of clinical symptoms for a long time. The low incidence of gastric cancer did not justify screening endoscopy, from both a clinical and economic point of view [1]. On the other hand, in Eastern countries gastric cancer still presents a high incidence and endoscopic diagnosis of early lesions is one of the most important rationales of the procedure [2]. The gastric cancer screening program was launched in Japan in 1960, with barium-meal gastric photofluorography. The diagnosis of early lesions is still possible with this procedure [3], but endoscopy is increasing in relevance.

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## 4.2 How

The retrospective endoscopic evaluation of advanced disease developed during the screening program led Japanese researchers to clearly define subtle changes of the mucosa as early gastric lesions, visible only after the use of a dye-spraying technique with indigo carmine. This approach clearly demonstrated some key points: conventional endoscopy was not enough for the diagnosis of early lesions; the exploration of the stomach needed a specific and accurate preparation with continuous photographic documentation of the gastric mucosa; precursors can show a non-polypoid (flat and depressed) appearance with different biological clinical behaviors in comparison with polypoid lesions [4]. The correct technique for an accurate exploration of the gastric mucosa includes three steps: preparation of the patient, use of anti-peristaltic agents and mapping of the entire stomach after adequate insufflation and desufflation, irrigation with water and defoaming agents [5]. Incomplete visualization of the entire gastric surface seems to be the main cause of missed lesions, as highlighted by a meta-analysis showing that the rate of missed gastric cancers can reach 9.4% in the case of negative UGE repeated over time, going up to 23.3% in the case of missed synchronous lesions [6]. Japanese authors proposed a systematic screening protocol for the stomach (SSPS), a sort of gastric mucosa scanning, through the acquisition of pictures of three- or four-quadrant views both clockwise and counter-clockwise [7]. On the other hand, the protocol proposed by the European Society of Gastrointestinal Endoscopy (ESGE) includes only four pictures of the stomach [8]. Even though a standardized protocol worldwide is still lacking, it is evident that the more time is spent exploring and documenting the gastric surface, the better are the clinical results.

## 4.3 With What?

Detection and characterization of suspicious lesions are so far the two main steps for a correct diagnosis of superficial neoplastic lesions.

White light imaging (WLI) can have optimal results in detecting abnormalities of mucosal surface structure and/or color only with an adequate gastric preparation. The typical reddish color is in fact due to an increased tumor-induced vascular density, while a pale appearance is related to neoplastic infiltration with increased glandular density [9]. Changes in light reflection and spontaneous bleeding are other important markers. Once a suspicious area has been detected, chromoendoscopy (CE) with indigo carmine 0.4% or a mixture of acetic acid 0.6% plus indigo carmine 0.4% (AIM) can enhance the surface features and sometimes the border of the lesion (Fig. 4.1). Therefore, the correct steps to detect a gastric lesion are: washing the mucosa with water plus simethicone, applying dye solution (10 mL) for about 1 min and washing gently again. In cases of a well-demarcated lesion with coexisting irregularity in color/surface pattern, the diagnosis of early gastric cancer, intestinal type, is highly suspicious. A meta-analysis confirmed that CE has a high

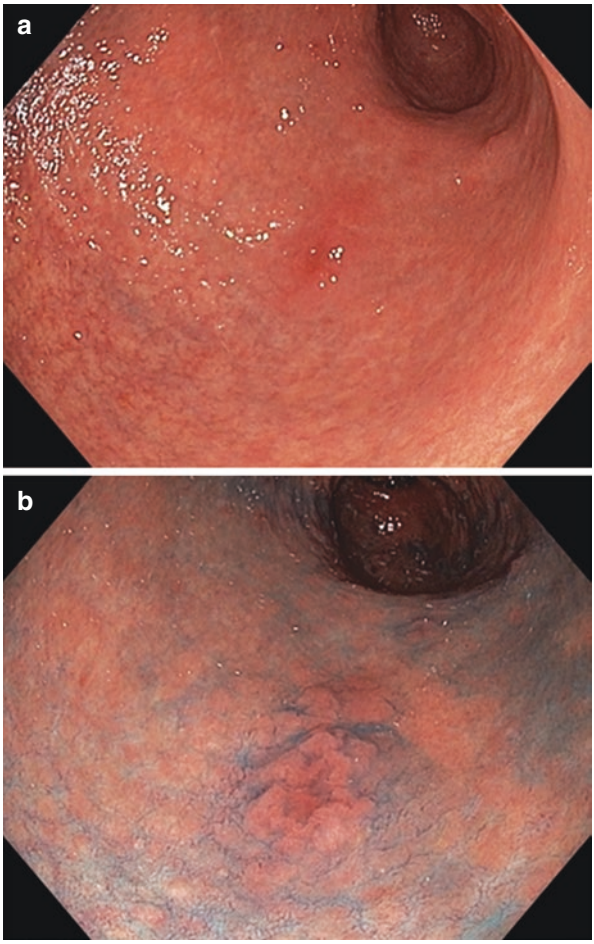


**Fig. 4.1** High-grade dysplasia: (**a**) white light imaging; (**b**) chromoendoscopy

diagnostic accuracy in detecting premalignant gastric lesions and early gastric cancer, compared to standard white light endoscopy [10].

The second step of the procedure aims to characterize the lesion and is based on high-definition endoscopy, which can presume histological diagnosis and document a possible submucosal invasion of the lesion [11]. The color charge-coupled device system includes a magnification up to 2 mm distance from the epithelial surface, yielding an optical 40× magnification in dual-focus mode. With dual focus endoscopes (e.g., GIF-H190Q or CF-H190Q for Exera III of GIF-HQ290 or CF-HQ290 for Lucera Spectrum, Olympus) the operator can switch between standard mode and near mode (40×) for close observation with a depth of field of 2–6 mm. In combination with the 1.5 digital zoom, these endoscopes offer 60× magnification. The multi light system (Eluxeo, Fujifilm) even allows to switch from standard WLI or bioluminescence imaging (BLI) to high-power magnifying (100×) WLI or BLI to obtain high resolution image-enhanced endoscopy (IEE) of micro-surface (S) or

micro-vascular (V) structures. A soft black hood mounted as a distal attachment on the zoom endoscope can keep precise distance from the lens for clear focused images. Underwater observation with high magnification (60×−120×) improves resolution, abolishes surface light reflection and favors acetic acid or AIM magnified CE in the evaluation of difficult or small lesions. Narrow band imaging (NBI) increases the contrast and enhances the visibility of structures (IEE) by changing the image color (Fig. 4.2). NBI is based on hemoglobin absorbance and produces images of the microvessels in the superficial mucosal layer (lamina propria) and submucosa: the sharpness of NBI imaging depends on the index of hemoglobin color enhancement. The structure enhancement function improves image resolution on magnifying observation in Olympus Lucera CV-260LS and Exera CV-190 video processors. There are two modalities, A and B, each with eight levels, and three of them can be preset. The Eluxeo system (Fujifilm Corp, Tokyo) also has mode A and B with nine levels for BLI. The default setting for BLI is B4 for both standard and

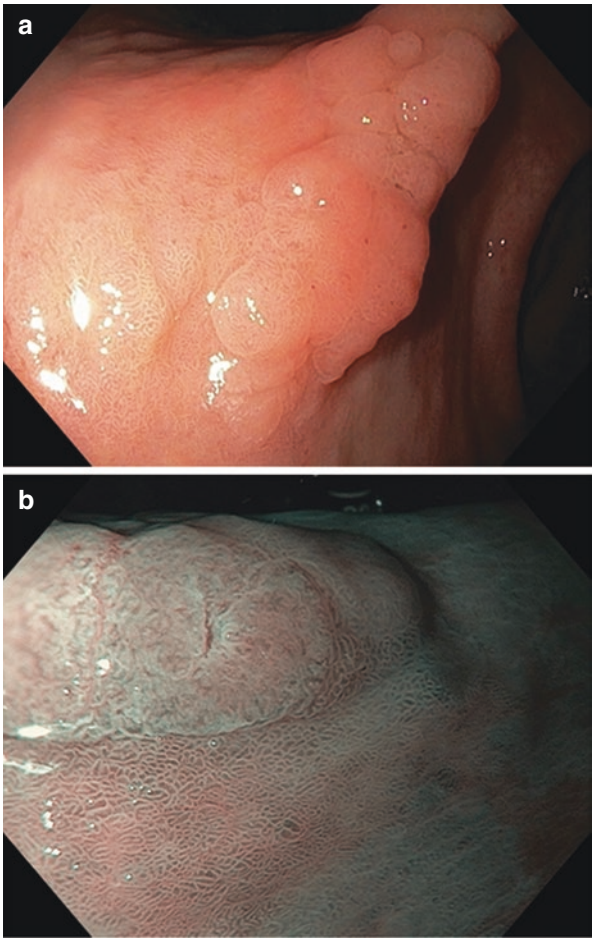


**Fig. 4.2** Well-differentiated T1a adenocarcinoma: (**a**) white light imaging; (**b**) narrow band imaging

magnification views. The post-imaging digital filter technique (i-Scan, Pentax) needs tuning for enhancement of surface structure (SE mode) or of green-blue spectral bands for "tone enhancement" (TE mode). Modern endoscopy with the combination of NBI plus magnifying observation involves the possibility of defining the microvascular pattern and micro-surface pattern. Japanese authors proposed a diagnostic system, the VS (Vessel plus Surface) classification system, which proved to be a promising technique for characterizing small or flat early lesions with diffuse or undifferentiated type histology. Both the patterns can be regular, irregular or absent. So far at the end of the visualization there are two main possible findings: irregular vascular and/or surface pattern with a possible demarcation line of the lesion and, if one or both are positive, the diagnosis of early GC is fulfilled in 97% of the cases [12].

## 4.4 Bite What?

Biopsy specimens should be taken from both the suspicious area and from the borders of the lesions in order to choose the best treatment option. Furthermore, histological examination aims at assessing the presence of pre-neoplastic lesions, as well as early or advanced gastric adenocarcinoma. The histological report must therefore provide information about a possible *Helicobacter pylori* infection, gastritis staging according to the OLGA-staging system, the histotype and the GC grading in the case of adenocarcinoma [13]. As previously mentioned, in Western countries GC is usually detected at advanced or metastatic stage. Surprisingly, mixed types of advanced cancer may coexist in the same lesion, such as intestinal or diffuse adenocarcinoma according to the Laurén classification. This is mainly due to the disease-specific inter-tumor heterogeneity. The molecular classifications of GC clearly highlight how tumors belonging to the same Laurén group can have different behaviors, reflecting alternative biological activation pathways. This opens new frontiers for medical or surgical treatment. Indeed, the medical treatment should be modulated with chemotherapy or immunotherapy, while surgery should contemplate less invasive resection modalities with the potential opportunity for patients to receive tailored treatments. Currently, trastuzumab in combination with chemotherapy is the standard option for patients with HER2-positive metastatic GC [14]. Therefore, the assessment of HER2 status is mandatory to choose these therapeutic modalities. Yoshida et al. showed how the concordance rate of immunohistochemistry and fluorescence in situ hybridization HER2 results, between endoscopic biopsies and resected specimens, were 57.0% and 72.7%, respectively [15]. These results highlight the potential difficulty in evaluating the HER2 status of the tumor at the time of diagnosis. The presence of tumor necrosis and deep ulcerations, together with the intra-tumor heterogeneity could explain the histological discrepancy between preoperative biopsies and histology performed on the surgical specimen. These results allow us to speculate that these outcomes may be present not only in cases of HER2 but also other tumor markers such as Epstein-Barr virus and microsatellite instability, limiting the therapeutic opportunities available for the patients. The literature

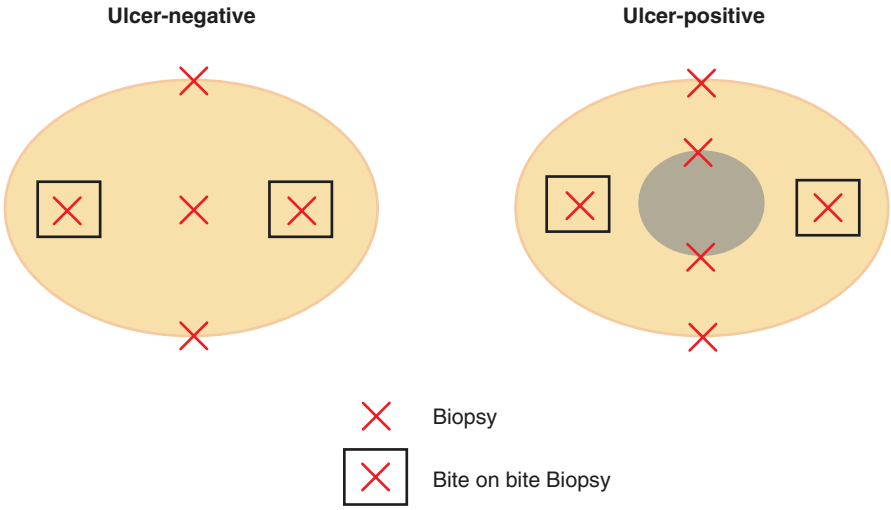


**Fig. 4.3** Proposed biopsy protocol: two biopsies at the margin of the lesion; one biopsy in the center of an ulcer-negative lesion, or two biopsies at the margin of the ulcer in an ulcer-positive lesion; and two superficial and two deep biopsies at midpoints between the center and the margin of the lesion

reports different biopsy protocols for different conditions, as for patients with gastritis, Barrett's esophagus and CDH1 gene mutation. In our opinion, also in cases of advanced GC a biopsy protocol should be conceptualized in order to obtain the most accurate biopsy sampling of the entire tumor, with an adequate number of targeted biopsies (Fig. 4.3).

## 4.5 Conclusion

A well-performed endoscopy is crucial both to diagnose early, difficult to identify, lesions and to correctly characterize macroscopic lesions. To comply with this mandate, it is necessary to follow some suggestions: prepare the patient; clean the stomach; take pictures; use at least WLI with CE; and bite right. In summary: keep calm and take your time.

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# Hereditary Gastric Cancer: A New Syndrome

5

Giovanni Corso, Francesca Magnoni, Cristina Trovato, Antonia Girardi, Raquel Seruca, Joana Figueiredo, and Franco Roviello

## 5.1 Introduction

The first description of *CDH1* germline mutation was reported in Maori kindred and families with diffuse gastric cancer (DGC) and lobular breast cancer (LBC) aggregation [1]. In 1999, the International Gastric Cancer Linkage Consortium (IGCLC) defined the hereditary diffuse gastric cancer (HDGC) syndrome and established clinical criteria for *CDH1* genetic screening of individuals and families at risk [2]. Using those first guidelines, the detection rate of *CDH1* mutations was approximately 40% [3]. However, the guidelines were subsequently revised given that *CDH1* germline mutations were also identified in individuals who did not meet

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testing criteria [4–6]. Hansford et al. reported that in individuals meeting the IGCLC 2010 criteria [5], the cumulative lifetime risk of gastric cancer at 80 years of age was 70% (95% CI, 59–80%) for males and 56% (95% CI, 44–69%) for females, whereas the breast cancer lifetime risk for females was 42% (95% CI, 23–68%) [7].

To date, several *CDH1* mutations affecting the entire coding sequence and functional domains have been identified in the context of HDGC [7, 8]. Whereas the majority of HDGC patients display *CDH1* truncating mutations that induce a deleterious effect and are thus a *bona fide* cause of DGC, around 20% harbor mutations of the missense type, which represent a major clinical challenge.

It has been estimated that HDGC accounts for only 1% of all diagnosed gastric cancers, but this small proportion represents a very complex syndrome, due to its difficult clinical and molecular management. In this chapter we will address these different aspects to improve understanding and translation in clinical practice.

## 5.2 *CDH1* Gene and E-Cadherin Protein

The *CDH1* gene (OMIM no. 192090) is located on chromosome 16q22.1 and encodes for the E-cadherin protein [9]. This macromolecule is a transmembrane glycoprotein expressed on epithelial tissue and is responsible for calcium-dependent, cell-to-cell adhesion [10]. E-cadherin is critical for establishing and maintaining polarized and differentiated epithelia through intercellular adhesion complexes. The human E-cadherin function is to suppress cell invasion; in fact its deregulation is correlated with the infiltrative and metastatic ability of the tumor [11], with the consequent loss of cell adhesion and concomitant increase in cell motility [12]. In human samples, somatic *CDH1* alterations are associated with poor survival and worse prognosis in gastric cancer patients [13].

## 5.3 Updated Clinical Criteria

Clinical criteria for the definition of HDGC syndrome were established in the last IGCLC meeting [14] and, in particular, *CDH1* testing is recommended when one of the following criteria have been met and following confirmation of cancer diagnoses:

**Family Criteria**

(a) ≥2 cases of gastric cancer in family regardless of age, with at least one DGC;
(b) ≥1 case of DGC at any age and ≥1 case of LBC at age <70 years in different family members;
(c) ≥2 cases of LBC in family members <50 years of age.

**Table 5.1** Mutation types identified within study groups

| Mutation type | Series study | Family study | Unknown study | Total | *p*-Value* |
|---|---|---|---|---|---|
| Deletion | 46 (24.6%) | 77 (21.6%) | 4 (20.0%) | 127 (22.6%) | 0.05 |
| Insertion | 9 (4.8%) | 46 (12.9%) | 3 (15.0%) | 58 (10.3%) | – |
| Non-sense | 36 (19.3%) | 85 (23.9%) | 4 (20.0%) | 125 (22.2%) | – |
| Missense | 54 (28.9%) | 71 (19.9%) | 6 (30.0%) | 131 (23.3%) | – |
| Splice-site | 41 (21.9%) | 77 (21.6%) | 3 (15.0%) | 121 (21.5%) | – |
| Imbalance | 1 (0.5%) | 0 (0.0%) | 0 (0.0%) | 1 (0.2%) | – |
| Total | 187 (33.2%) | 356 (63.2%) | 20 (3.6%) | 563 | – |

From [15] (published under the terms of the Creative Commons CC-BY license)
*$p$-Value from Chi-square excluding imbalance mutation type

**Individual Criteria**

(d) DGC at age <50 years;
(e) DGC at any age in individuals of Maori ethnicity;
(f) DGC at any age in individuals with a personal or family history (first-degree relative) of cleft lip or cleft palate;
(g) history of DGC and LBC, both diagnosed at age <70 years;
(h) bilateral LBC, diagnosed at age <70 years;
(i) gastric in situ signet ring cells or pagetoid spread of signet ring cells in individuals <50 years of age.

## 5.4 *CDH1* Mutation Frequency

Recently we conducted a systematic study to assess the overall *CDH1* germline mutations reported worldwide. We classified the published studies as "series study", "family study", or "unknown study", according to whether or not the *CDH1* testing criteria were adopted.

A total of 563 *CDH1* germline mutations were identified: 33.2% in the series study group, 63.2% in the family study group, and 3.6% in the unknown study group [15]. The mutation types identified within each study group are shown in Table 5.1.

## 5.5 Pathology

DGC with signet-ring cells is the predominant histologic type in carriers of *CDH1* germline mutations. In advanced stages, HDGC is indistinguishable from sporadic DGC; conversely, "early" stage HDGC is characterized by the presence of multiple foci of diffuse-type, signet-ring cell carcinoma (SRCC) confined to the superficial gastric mucosa [16].

Carneiro et al. proposed a histologic model for gastric cancer development in E-cadherin mutation carriers: at the beginning, histopathologic analysis shows a pattern of *in situ* SRCC with early pagetoid spread. Subsequently, early invasion is followed by overt pagetoid proliferation of signet-ring cells, and lastly, invasive SRCC is evident [17].

Macroscopic examination and sampling of prophylactic gastrectomies should follow specific protocols, and the histological examination should be made using a checklist [5].

Gross examination of prophylactic total gastrectomy samples revealed HDGC lesions in only a minority of cases, encompassing pale patches, nodules, and tiny ulcers/scars. The majority of total gastrectomies from *CDH1* carriers exhibit tiny mucosal foci of SRCC or *in situ* SRCC, although sometimes these were only discovered after careful review by an expert pathologist [18].

The application of the total-embedding protocol considerably increased the number of HDGC lesions identified. These findings argue in favor of the use of the total-embedding protocol and the thorough histopathological examination of the entire gastric mucosa, as the gold standard practice for the evaluation of total gastrectomy specimens from *CDH1* carriers.

## 5.6 Singularities of *CDH1* Missense Variants

Missense variants are subtle alterations in genetic terms, still they yield clinical phenotypes similar to those caused by truncating mutations, including familial aggregation of gastric cancer, LBC and cleft lip/palate abnormalities [6, 7, 19]. In light of current knowledge, no genotype-phenotype correlations can be established based on mutation type, domain affected or amino acid substituted [19].

The consequences of missense variants arise through distinct mechanistic effects encompassing protein misfolding and premature degradation, trafficking deregulation, aberrant glycosylation, and activation of oncogenic signaling pathways [20–24]. The multiplicity of these effects may underlie cancer cell plasticity and, consequently, different severity grades.

In the last two decades, several attempts have been made to improve variant interpretation and management of germline carriers [21, 25–30]. Accordingly, Lee et al. have described *CDH1* specifications for the variant curation guidelines proposed by the American College of Medical Genetics and Genomics, and the Association for Molecular Pathology (ACMG/AMP) [31, 32]. The recommendations were developed and validated following a systematic evaluation of variants obtained from a large cohort of clinical laboratory data [31]. Nevertheless, most of the rule specifications are not recommended for use in missense changes and a large proportion of variants remain unclassified. A comprehensive approach combining multiple lines of evidence is thus crucial to estimate the clinical relevance of novel missense alterations. In this sense, familial and population data, as well as *in silico* and *in vitro* evidence should be collected and further explored [5, 33] (Fig. 5.1).

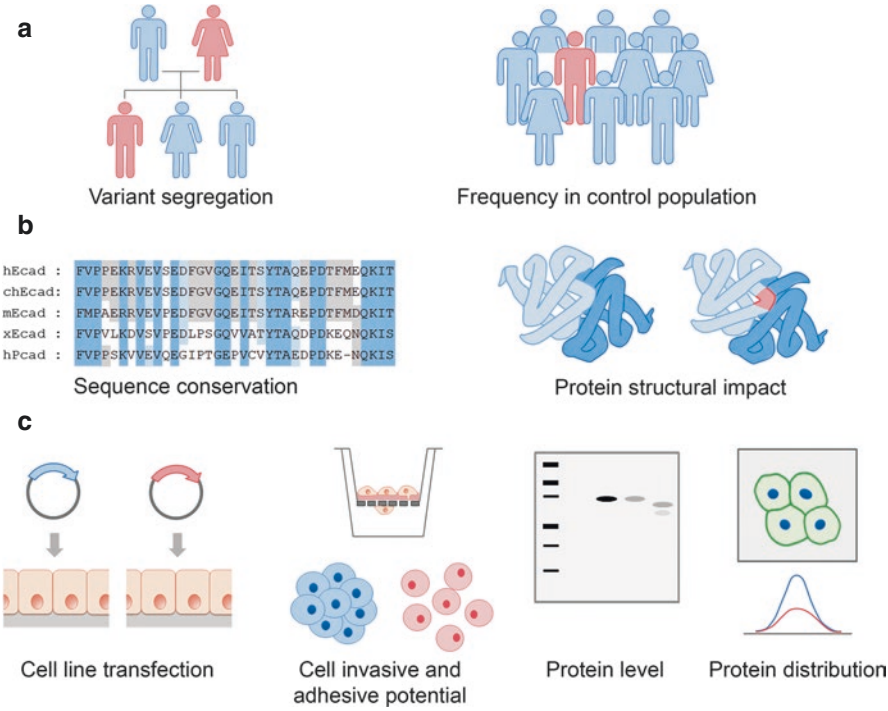


**Fig. 5.1** Proposed approach for missense variant classification. (**a**) Variant frequency in control populations and its segregation within pedigrees are important genetic parameters to determine the significance of missense variants. (**b**) *In silico* analyses evaluate sequence conservation across species and can estimate putative effects on protein structure. (**c**) Functional studies include the transfection of cell lines with the variant and the wild-type E-cadherin form and thereafter the assessment of protein levels, distribution patterns, as well as invasive and cell-cell adhesive capacities

Mutation frequency in healthy control populations, co-segregation of mutation with the disease within pedigrees, and mutation recurrence in unrelated families are important genetic parameters to evaluate disease risk [26]. Regarding variant frequency in different ethnic groups, one should be aware that databases can be poorly curated and have limitations including low-quality data, or lack of details on study origin and context [32]. *In silico* tools are advantageous to predict the degree of conservation of mutated amino acids within species, impact on splicing, and putative effects on protein structure [21, 26]. For this approach, several programs should be tested as different outputs can be achieved, depending on the selected algorithm [21, 26]. Likewise, current structural models were built using *Xenopus* and mouse data and do not cover the juxtamembrane region, which affects prediction performance [21]. In contrast, experimental strategies can determine the functional impact of missense alterations in up to 85% of the cases [8]. Despite the low throughput and associated technical limitations, *in vitro* assays using cell lines transfected with vectors encoding the variant and the wild-type protein allow investigation at the protein expression level, intracellular localization and main E-cadherin functions—cell-cell

adhesion and invasion suppression [28–30, 34]. Exceptionally, analysis of migratory patterns and of the cadherin-catenin interplay can also be applied [28, 34, 35]. Demonstrative of the urge to solve this issue, efforts have been made to develop *in vivo* models that better mimic the disease context (personal communication Seruca's Lab).

Overall, the classification of *CDH1* missense variants remains a challenge for future research. In this context, the establishment of an accurate analytical pipeline and its subsequent validation, based upon clinical and pathological evidence, will have a major impact on patient monitoring and treatment.

## 5.7 Prophylactic Total Gastrectomy

Prophylactic total gastrectomy (PTG) has been suggested as the treatment of choice for carriers of *CDH1* mutations, because of the lack of effective endoscopic screening and surveillance programs.

PTG can be performed either laparoscopically or open, based on the experience of the surgeon. Intraoperative frozen section of the resection margins is recommended to ensure that no gastric mucosa has been left behind. An extended D2 lymphadenectomy is not required and is generally discouraged to minimize postoperative morbidity. Instead, a D1 lymph node dissection is usually recommended. Regarding the reconstruction technique, a jejunal pouch reconstruction has been suggested by some surgeons but there are no clear data indicating advantages of this more complex technique over a standard direct Roux-en-Y, which is generally preferred [18].

Finally, the IGCLC recommended gastric surveillance instead of a PTG in pathogenic variant carriers with an unclear risk for DGC, and in individuals with a family or personal history of DGC and a *CDH1* variant of uncertain significance (VUS), and affected family members from HDGC-like families and their first-degree relatives [14].

To date, we identified 224 surgical procedures classified as PTG, with an age range of 18–71 years old. The majority of PTGs were performed in the USA (111; 49.6%) followed by the Netherlands (40; 17.8%), Canada (28; 12.5%), Belgium (8; 3.6%), Spain (8; 3.6%), Denmark (7; 3.1%), Portugal (6; 2.7%), Austria (6; 2.7%), Mexico (4; 1.8%), Iran (2; 0.9%), Australia (1; 0.4%), Chile (1; 0.4%), Germany (1; 0.4%), Hawaii (1; 0.4%), and Italy (1; 0.4%) (unpublished data).

## 5.8 Endoscopy

The primary goal of surveillance endoscopy is to assess for gastric mucosal changes that may signal progression of early cancer foci and exclude more infiltrative (>T1a) lesions. In addition, results of surveillance endoscopy can provide patients the opportunity to make more informed decisions about gastrectomy. Unfortunately, endoscopic detection of SRCC in *CDH1* carriers is poor, and histological evaluation

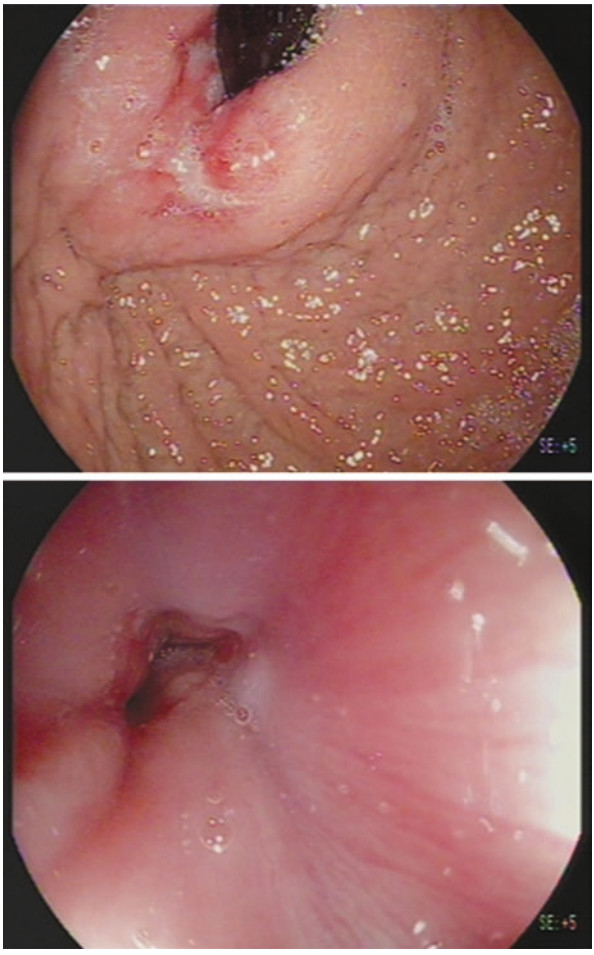

**Fig. 5.2** Patient *CDH1* germline mutation carriers presenting pT3N1 stage cardias gastric cancer. Cardias of modestly padded appearance where the known ulcerated neoplasm is observed with fine irregularities involving the mucosa up to the Z line

of surgical specimens demonstrates cancer foci in up to 45–60% of cases with a negative endoscopic evaluation [36, 37].

The main factor that hinders the endoscopic diagnosis of early DGC is that the tumor cells begin infiltrating the mucosa, while preserving a normal surface epithelium. Thus, endoscopy findings can remain normal until late stages of the disease leading to a delay in the diagnosis and a very poor prognosis (Fig. 5.2). Moreover, SRCC foci can be sparse (less than 2% of the gastric mucosa) and each focus is very often less than 1 mm in greatest diameter [38].

According to consensus guidelines, individuals who tested positive for a *CDH1* mutation should be advised to consider prophylactic gastrectomy regardless of any endoscopic findings [5]. However, some patients, despite carrying a pathogenic variant, elect to delay or not pursue the surgical intervention due to personal and psychological preferences. In that case and for those carrying a VUS or fulfilling the HDGC criteria without having a germline *CDH1* mutation, annual endoscopy

surveillance starting at age 20 or at the cut-off of 5 years prior to the family's earliest cancer diagnosis, following the Cambridge protocol and in experienced centers, is recommended even if the endoscopic approach is suboptimal [5, 39].

According to the IGCLC endoscopy surveillance protocol (Cambridge method), a careful examination in a dedicated session of at least 30 min with high-definition white light is recommended. Extensive washing of the mucosa with the assistance of mucolytic and anti-foaming agents is advised in order to allow for careful evaluation of the entire gastric mucosa. Since the lack of distensibility is a sign of an infiltrative process such as linitis plastica, repeated insufflation and deflation to maximize visualization of the entire gastric mucosa, and a check for distensibility is suggested.

Prior to obtaining random gastric biopsies, targeted biopsies of all suspicious lesions, in particular pale areas (considered more likely to have abnormal signet-ring cells), erythema, erosion, or other gastric abnormalities should be taken. After sampling of all visible lesions, five random biopsies should then be taken from each of the six anatomic regions (prepyloric, antrum, transitional zone, body, fundus, and cardia), with these groups of biopsies each being sent separately for pathological analysis [5]. Given the large number of biopsies performed, it is recommended to stop anticoagulation, if possible, prior to the procedure.

However, the Cambridge protocol of surveillance carries a high false-negative rate. A model developed by Fujita et al. estimated that for a 90% detection rate, the theoretical number of biopsies necessary is 1768 per patient, but this is not clinically feasible [40]. The main disadvantage of taking an extensive number of biopsies is the formation of scar tissue, which can then mimic the superficial pale appearance of SRCC lesions. Mi et al. showed that targeted biopsies (of typical pale lesions) can result in detection of SRCC foci in more than 40% of patients, yielding a sensitivity of 28% [41]. However, we have to consider other studies demonstrating that pale areas are very non-specific for SRCC [39, 42, 43]. In a recent paper, in a cohort of *CDH1* mutation carriers, SRCC lesions were identified by an extensive endoscopic surveillance protocol in 69% of SRCC-positive patients who underwent a gastric resection. In this paper the yield of targeted biopsies (11%) was much higher for identification of SRCC lesions than the yield of random biopsies (0.9%). The low number of SRCC detected through random sampling demands a critical reappraisal of random biopsy sampling in the IGCLC guideline [44].

Given its poor reproducibility and high false-negative rates, techniques of early gastric cancer surveillance other than the Cambridge method have been explored. Chromoendoscopy, which aids in identifying mucosal pale areas, was reported to improve SRCC detection rates; however, this technique is limited to detecting only larger cancer lesions. Moreover, due to concerns about dye toxicity, chromoendoscopic examination is currently not recommended as a standard of care for HDGC [5, 43, 45]. Autofluorescence and narrow-band imaging as adjuncts to white-light endoscopy and random biopsy do not appear to improve occult cancer detection. Endoscopic ultrasonography combined with the Cambridge method failed to demonstrate an improvement in the sensitivity of detection [46].

Further development of endoscopic techniques, such as electronic enhanced imaging techniques, confocal endomicroscopy, magnification and artificial intelligence, is warranted to improve the detection rate of SRCC foci.

Confocal endomicroscopy (CEM) is indicated for microscopic visualization of the mucosa during endoscopy at an approximately 1000-fold magnification, and might limit the sampling error of untargeted biopsies [47, 48]. A phase II clinical trial is currently underway to compare CEM to standard endoscopic gastric mapping in an effort to reduce the false-negative detection rate of SRCC in patients diagnosed with HDGC [49].

Despite no known association between *Helicobacter pylori* (*H. pylori*) and HDGC, baseline *H. pylori* testing on the gastric biopsy specimens is recommended given that *H. pylori* is considered a class I carcinogen by the World Health Organization. Subsequent treatment and confirmation of eradication in individuals who are *H. pylori*-positive is advised [50].

## 5.9 Lobular Breast Cancer

LBC is a morphological typology of breast cancer, comprising up to 15% of all cases of this cancer [51]. It represents a good prognostic phenotype, with low histological grade, hormone receptor positivity, and with a generally favorable response to endocrine therapy [51]. However, when it is associated with the E-cadherin dysfunction, it shows a cellular discohesive pattern and a loss in tissue basic structure, resulting in cellular unregulated growth, metastases and worse prognosis [52].

Several genetic studies have identified novel germline *CDH1* mutations in LBCs correlated with the HDGC syndrome [53, 54]; indeed, LBC is associated with HDGC, and E-cadherin constitutional mutations have been described in both gastric and breast cancers [55]. Thus, women with pathogenic *CDH1* variants present an elevated lifetime risk of invasive LBC, in addition to an increased risk of gastric cancer [56]: female *CDH1* mutation carriers meeting the IGCLC 2010 criteria [5] have in fact a risk of breast cancer of 42% (95% CI, 23–68%), mostly of them LBC [3, 7, 57].

Clinical management of heritable *CDH1* gene mutation carriers is challenging and the subject of extensive scientific debates and studies. The latest IGCLC clinical criteria established as mandatory for *CDH1* genetic screening include a personal or family history of HDGC and LBC, one diagnosed <50 years [5, 6]. Testing is also suggested in families with bilateral LBC or a family history of two or more cases of LBC <50 years [5, 6].

The IGCLC approved that E-cadherin genetic screening associated with LBC can be reconsidered in two different cancer inherited predispositions, both LBC in the setting of the HDGC syndrome, and hereditary lobular breast cancer (HLBC) not associated with gastric tumors [6].

Hence, *CDH1* germline mutations have been identified in cases of LBC not associated with the classical HDGC syndrome [58]. Therefore, a novel working group dedicated to the clinical and genetic management of HLBC has proposed new

criteria to identify patients at risk of HLBC: (a) bilateral LBC with or without a family history of LBC, with age at onset <50 years; and (b) unilateral LBC with a family history of LBC, with age at onset <45 years [6, 58].

At present, there is no shared or defined protocol for breast surveillance in *CDH1* mutation carriers: indeed, the literature does not document many cases of identified *CDH1* germline mutations and data concerning the breast cancer risk in these subjects are not substantial [58]. Meanwhile, the clinical genetic trial "Understanding how *CDH1* germline mutations affect HLBC" [59] is ongoing and aims to identify the role of *CDH1* in HLBC without DGC aggregation.

In mutated *CDH1* women, careful breast radiological monitoring is nonetheless recommended, due to the significant risk of LBC developing [54], even if there are no international guidelines on breast radiological surveillance in these individuals, unlike for ascertained *BRCA1/2* genetic mutation carriers [54]. Histopathological non-cohesive features of LBC make radiological diagnosis not easy on mammography [60, 61], with a reported sensitivity ranging between 57% and 81% [62–64]. Ultrasound and breast magnetic resonance imaging (MRI) play instead a more significant role in LBC detection, presenting a reported overall diagnostic sensitivity of between 68% and 98% [65], and 93% [66], respectively. Corso et al. recommended the use of annual breast MRI followed by mammography and ultrasound at six-month intervals, similar to the program established for *BRCA1/2* carriers [58]. Furthermore, updated clinical practice guidelines recommend starting breast surveillance for HDGC and HLBC at 30 years of age, with yearly MRI from 30 to 50 years of age, underlining the uncertain advantage of adding mammography in young women and the role of supplementary screening ultrasound in dense breasts, when MRI is not feasible [14].

When considering the risk management of *CDH1* mutation carriers, distinguishing between never-affected individuals and patients diagnosed with breast cancer should be a priority [18].

The recent American Society of Clinical Oncology (ASCO) 2020 guidelines revealed a de-escalation in breast surgery recommendations when LBC is detected, as both *BRCA* and moderate-penetrance gene mutations should be treated with breast-conserving therapy, when this is clinically appropriate [58, 67]. Insufficient data exist to recommend contralateral breast cancer risk-reducing surgery to affected *CDH1* mutation carriers [6] and prophylactic surgery to healthy individuals with *CDH1* mutation, even if also family history, ability to undergo high-risk screening procedures, and patient preference are major factors to be taken into account in the decision-making process [68]. Indeed, discussion on prophylactic surgery should be set up after genetic counselling, in a multidisciplinary context [6].

As there are currently no specific indications for prophylactic mastectomy, the chance of risk-reducing surgery should be discussed in relation to the potential presence of LBC in the personal clinical history of *CDH1* mutation carriers. A precise scheme on surgical management for *CDH1* carriers has been recently delineated: information on risk-reducing surgery should be provided to *CDH1* positive patients with a diagnosis of LBC, who have a clinical indication for mastectomy or already had a mastectomy as part of their cancer treatment [58, 69]. Likewise, prophylactic

surgery should be provided to individuals with a positive family history for LBC and a well-documented *CDH1* pathogenic alteration in a first-degree relative [58, 69].

The aim of prophylactic mastectomy is to achieve maximum risk reduction, removing completely all the breast gland. Skin- and nipple-sparing mastectomy with immediate reconstruction is deemed adequate [14]. On the basis of current evidence [58], as defined for *BRCA* mutation carriers, nipple-sparing mastectomy with immediate reconstruction represents the surgical procedure of choice, which preserves both the skin and nipple-areola complex, obtaining pleasant aesthetic results and psychological well-being, with excellent oncological safety and a low complication rate [70–73].

## 5.10 Conclusion

HDGC syndrome is likely a much more complex disease than what was initially thought. PTG remains the only life-saving approach for individuals carrying deleterious germline mutations and fulfilling the HDGC criteria. However, great caution is needed in the absence of a family history of gastric cancer. Prophylactic mastectomy should be discussed in *CDH1* carriers with a strong aggregation for LBC, fulfilling the established clinical criteria. In asymptomatic *CDH1* carriers who do not fulfill the clinical criteria, surveillance is preferred. Given the complexity and the rarity of this syndrome, *CDH1* carriers should always be treated in a multidisciplinary fashion and in highly specialized cancer centers.

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# Part II

# Staging

# Endoscopic Ultrasound Staging in Gastric Cancer

6

Alessia Santini, Ivano Biviano, and Raffaele Macchiarelli

## 6.1 Introduction

Gastric cancer represents the fifth most common malignancy and the third leading cause of cancer mortality with widely varying incidence worldwide. Despite a progressive reduction of the incidence, it remains one of the most common malignant tumors in the gastrointestinal tract, with low rates of early diagnosis, radical resection and 5-year survival [1].

Adequate tumor staging is essential to define the most appropriate therapeutic strategy and provide accurate pre-treatment risk stratification. Gastric cancer can be divided into early- and advanced-stage. Early gastric cancer is defined as invasive gastric cancer that invades no more than the submucosa, irrespective of lymph node metastasis and lesion size, while in advanced-stage disease the cancer invades beyond the submucosa. The most commonly used clinical staging classification system for gastric cancer is the TNM system, used by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC). Japan has a different staging system for gastric cancer, based on the location of involved lymph nodes around the stomach. This is different from the U.S. system, which uses the number of lymph nodes and not their location. The staging system of gastric cancer has been revised with the recently issued Japanese Classification of Gastric Carcinoma 15th edition, and the UICC TNM classification 8th edition [2, 3].

Over the years, the approach to early lesions has been refined with the development of advanced endoscopic resection techniques, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), leading to the need

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to better identify early gastric lesions. Early gastric cancer has a much higher prevalence in the Far East, especially Japan, and the prognosis is very encouraging, with 5-year survival rates greater than 90% in Asia and greater than 80% in Western countries [4, 5].

## 6.2 The Role of Endoscopic Ultrasound

Endoscopic ultrasound (EUS) performed prior to any treatment is important in the initial clinical staging of gastric cancer [6] and can improve the diagnostic accuracy of stage T, particularly in discriminating T1a from T1b or T2. It may be useful for evaluating the presence of abnormal or enlarged lymph nodes susceptible to cancer (N assessment), while not so necessary in advanced forms (T3–T4 tumors), and may occasionally find its place in inadequate computed tomography (CT) examinations and to detect signs of spread, such as lesions in surrounding organs or the presence of ascites [7].

In a 2015 Cochrane review, Mocellin et al. found that EUS can distinguish between superficial (T1–T2) and advanced (T3–T4) primary tumors with a sensitivity and specificity greater than 85% and that the accuracy of EUS can be considered clinically useful for clinicians in the locoregional staging of gastric cancer, although heterogeneity is observed in studies and further investigations are needed to identify the factors influencing the outcome of this tool [8].

EUS is moreover indicated in cases of diffuse gastric cancer with negative biopsies; to determine the proximal and distal limits of the tumor; for diagnosis of the lymph nodes with the ability to perform fine-needle aspiration biopsies for cytologic examination; before neoadjuvant chemotherapy [9].

Merkow et al. analyzed 734 patients treated for gastric cancer to assess the agreement between EUS and the pathological result. The agreement was considered moderate (stage T 52% and stage N 70%). The accurately estimated risk of invasion was 73%, overestimated in 19% and underestimated in 8%. The report concluded that EUS should be used with caution and when necessary, always in combination with another diagnostic imaging method [10].

A 2017 meta-analysis found that EUS may be superior to multidetector computed tomography (MDCT) in early preoperative lesions [11]. These data were recently supported by a network meta-analysis comparing the diagnostic accuracy of EUS vs. EUS + MDCT in a total of 1859 patients (1302 males) with gastric adenocarcinoma. The authors showed that in stage T1 the sensitivity of EUS was significantly higher than that of MDCT (43.88 vs. 26.77, 95% CI), while no significant differences were observed in stages T2–T4. For the N stages the data were not sufficient, but for stage N1 the sensitivity and specificity of EUS and MDCT were comparable ($p = 0.68$ and $p = 0.98$, respectively). However, the N stage should be carefully assessed by both methods and MDCT proved to be more efficient for

advanced stages. For stage T1 the authors also compared EUS and EUS + MDCT and they concluded that even though diagnostic accuracy improves with the use of both techniques, sensitivity and specificity are not relevant [12].

These data reinforce the AJCC recommendation which suggests the use of EUS in the assessment of the early clinical stage of gastric cancer [13].

## 6.3 Endoscopic Ultrasound Technique and Findings

Gastric cancers that are located within 5 cm of the gastroesophageal junction that also cross the junction are staged as esophageal cancers.

Ultrasound imaging of the gastric lining is obtained by using radial echoendoscopes with frequencies ranging from 5 to 12 MHz and color Doppler capabilities. Study of the gastric wall is possible by applying the transducer directly to the gastric wall, or scanning after filling the gastrointestinal lumen with water, or applying a water-filled balloon over the transducer.

However, when the transducer is in direct contact with the gastrointestinal wall, compression could distort the image, so the best images are obtained through luminal water. This method allows one to distinguish the typical five-layered sonographic pattern and easily detect any pathological alteration.

In some cases, as in gastroesophageal junction, water filling is not possible. A water-filled balloon, placed over the tip of the endoscope at the level of the transducer, allows both an improved acquisition of ultrasound images and a better stability of the instrument [14].

The superficial gastric mucosa is represented by an echogenic first layer, and the deeper mucosa by a hypoechogenic second layer; the submucosa is represented by an echogenic third layer, the muscularis propria as a hypoechogenic fourth layer, and the serosa as an echogenic fifth layer (Figs. 6.1 and 6.2).

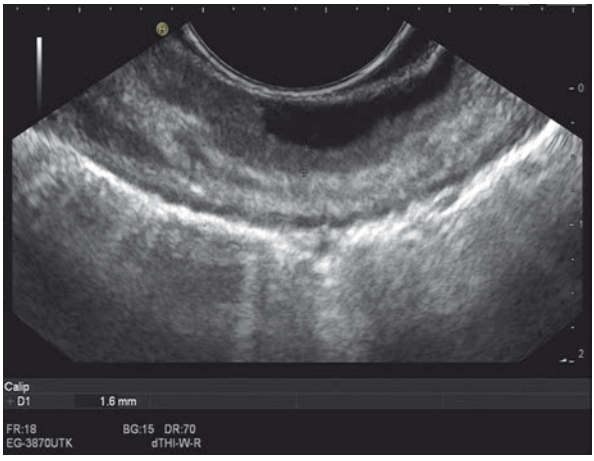


**Fig. 6.1** Endoscopic ultrasonography imaging of early gastric cancer, without invasion of lamina propria

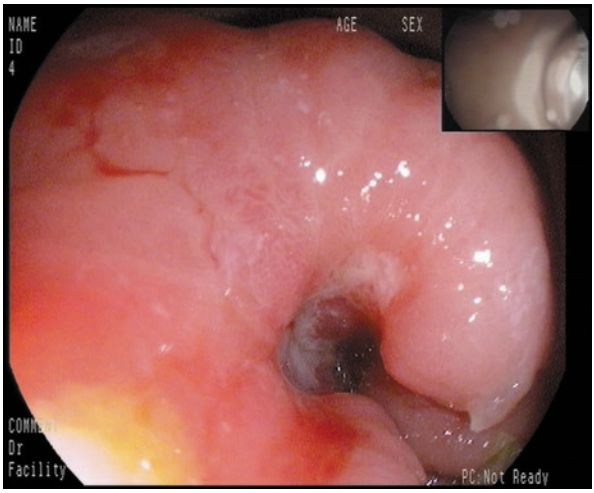


**Fig. 6.2** Endoscopic ultrasonography evaluation of gastric cancer

Gastric carcinomas generally appear on ultrasound as hypoechoic lesions with fuzzy margins, originating from the mucosal layers with gradual loss of the stratified pattern of the normal gastric wall corresponding to greater depths of tumor penetration. T1 lesions are limited to the mucosa (T1a when the lesion invades the lamina propria) or can penetrate the submucosa (T1b). T2 lesions reach the muscularis propria, without crossing it, causing an irregular outer border related to the invasion of the subserosa. In T3 lesions, the hypoechoic area extends through the serosa. T4 lesions invade the visceral peritoneum (T4a appears as loss of the clear line recognized as the serosa), or a local organ (T4b such as liver, pancreas, spleen, diaphragm) or a large vessel (aorta, celiac axis).

Lymph node assessment requires scanning at 5.0–7.5 MHz. Malignant lymph nodes are generally round in shape, well-defined, with homogeneous hypoechoic appearance and usually without an echogenic hilus (Fig. 6.3). Diagnosis of malignant lymph nodes can be confirmed with the use of fine-needle aspiration biopsy (FNAB) for cytological evaluation. FNAB should be done if it can be achieved without crossing an area of the primary tumor or major blood vessels. FNAB is not always necessary, but it should be performed to confirm the diagnosis in patients with early disease with suspicious malignant lymph nodes, or when there is a diagnostic doubt with a reactive lymph node. In addition, if the presence of ascites has been identified, FNAB should be obtained to rule out peritoneal spread of the disease [15].

Another useful application, during EUS, is elastography, which is able to analyze the elastic properties of lymph node tissue (Fig. 6.3). Elastography can help distinguish harder (usually malignant) tissue that appears blue, with high accuracy, and target the most suspicious area for biopsy [16].

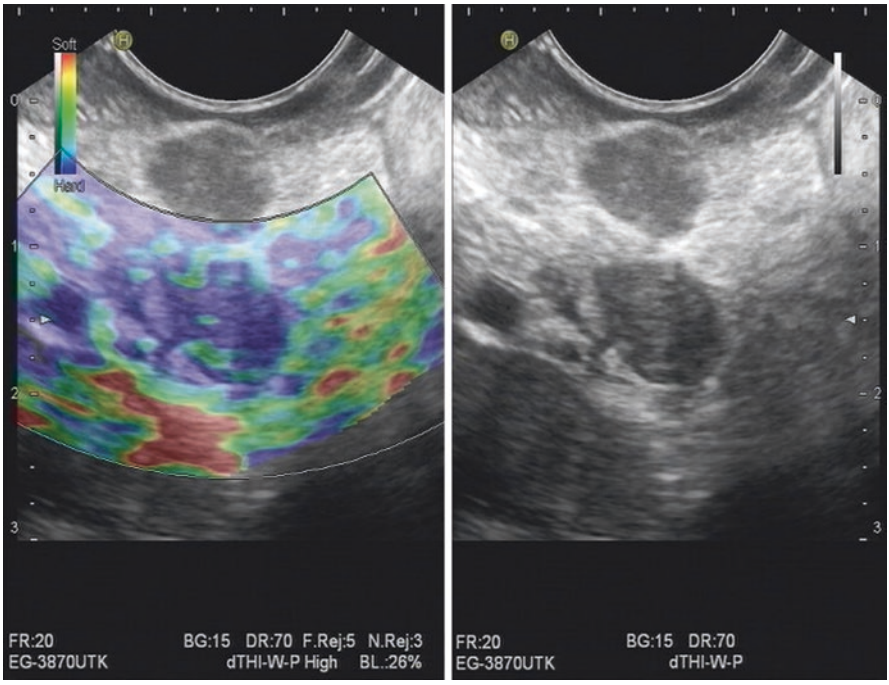


**Fig. 6.3** Endoscopic ultrasonography imaging of round, sharply demarcated and hypoechoic malignant lymph nodes, also evaluated by elastography

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# CT and PET/CT Scans in Gastric Cancer Diagnosis

7

Maria Antonietta Mazzei, Francesco Gentili, Frida Pittiani, Laura Romanini, and Luca Volterrani

## 7.1 Introduction

One of the critical questions is always how important the role of imaging in multidisciplinary decision-making for gastric cancer (GC) treatment is. Although surgery remains the mainstay of therapy in GC, in recent years there has been relevant progress in endoscopic treatment of early forms, whereas in locally advanced GC ≥T3 (meaning a cancer that involves the serosa) or in any nodal involvement the standard treatment in Western countries is surgery combined with neo-adjuvant chemotherapy [1–3].

In advanced unresectable/metastatic GC (35–40% of cases at the time of the first diagnosis), chemotherapy is considered the standard treatment. At the same time, the introduction of new anticancer agents and of polychemotherapy regimens has made macroscopic complete resection possible in some metastatic/unresectable GC before therapy. This type of surgery, known as "conversion surgery", is defined as a surgical treatment with the goal of R0 resection in initially unresectable GC patients after response to chemotherapy; it therefore has a curative intent, and differs from palliative surgery [4].

Furthermore, in selected cases with peritoneal carcinomatosis (PC), radical gastrectomy associated with cytoreductive surgery and hyperthermic intraperitoneal

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chemotherapy (HIPEC) can be performed, with significant advantages in overall survival and peritoneal recurrence rates [5].

The treatment of GC has become highly complex and multimodal and the entire decision-making process is largely driven by imaging and in particular by computed tomography (CT).

Combined positron-emission tomography/computed tomography (PET/CT) has been recently investigated for staging GC, but its sensitivity is low for Laurén's diffuse types and the spatial resolution of fused CT images is poor if compared to contrast-enhanced CT alone [6].

## 7.2 Detection of Metastatic Lesions

At the time of staging, imaging is aimed at separating patients who can benefit from upfront surgery from those who need a chemotherapy treatment, whether for neoadjuvant, palliative or conversion purposes. However, imaging plays a fundamental role also at the time of re-staging, where it is aimed at evaluating the response to therapy.

First of all, imaging has to detect metastatic lesions (overall distant lymph nodes, liver or bone metastases) and, especially in GC, it has to detect PC, which could be synchronous (meaning at the time of diagnosis) in about 5–20% of cases and devious since it could be also present without ascites. In advanced GC, using imaging, and in particular CT, the radiologist has to evaluate resectability by ruling out the absolute criteria of exclusion for radical surgery (Table 7.1), even though the definition of resectability is not a general and reproducible model, since it may depend on surgeon experience and on anesthesia support [7].

In searching for PC, radiologists can benefit from knowledge of the GC histotype as PC is more frequent in Laurén's diffuse type, as well as from the technology available today, using dual-energy CT (DECT). Thanks to the selective increase in iodine attenuation at low energy values (40–70 keV), DECT could increase the density of lesions that concentrate iodine, improving the contrast enhancement with the surrounding structures, especially at the equilibrium phase for PC (Fig. 7.1) [8]. The last few years have seen a significant rise in the use of PET/CT for detecting PC; however, this modality is poorly sensitive in the case of small lesions and low peritoneal cancer index, so its use is not recommended in routine clinical practice [9].

**Table 7.1** Absolute criteria of exclusion for radical surgery

| |
|---|
| – Infiltration of left gastric artery |
| – Infiltration of hepato-duodenal ligament |
| – Infiltration of mesenteric root |
| – Infiltration of other organs (pancreatic head massively infiltrated) |
| – Presence of more than three hepatic resectable metastases in the same lobe or multiple bilateral metastases |
| – Infiltration of small bowel and its mesentery (expected small-bowel resection for more than one-third of the whole length) |

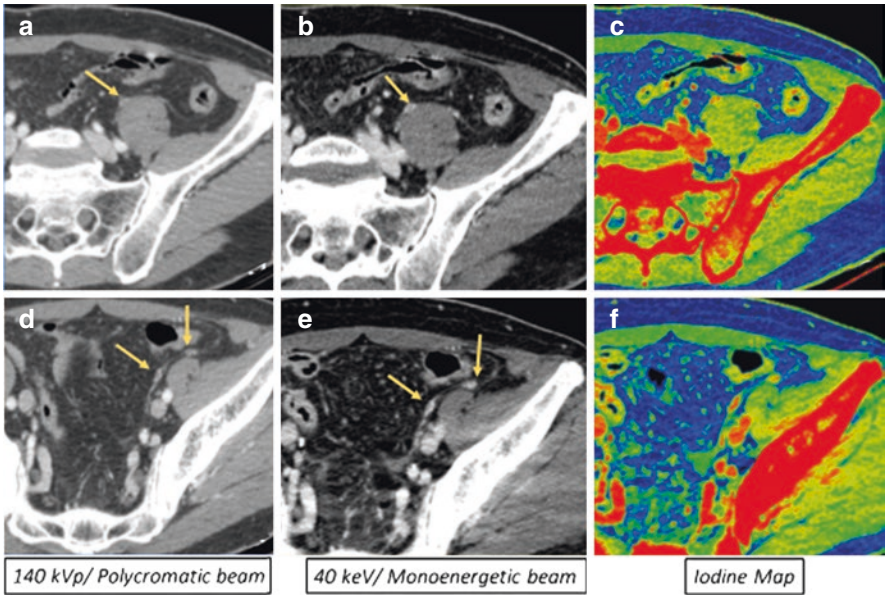


**Fig. 7.1** Small nodules of peritoneal carcinomatosis in a 67-year-old man with a diffuse Laurén type gastric cancer. If compared to standard computed tomography acquisition at 140 kVp (**a**, **d**), images at 40 keV (**b**, **e**) and iodine maps (**c**, **f**) derived from the dual-energy protocol improve contrast resolution and visualization of the lesions

The goal of imaging in the absence of metastatic disease in GC is to accurately stage the T and N parameters.

## 7.3 T Staging

Regarding the T parameter, the reasons why differentiation of the various T stages could be important for GC treatment decisions are the following: T1a from T1b for endoscopic resection, T1 from T2 for limiting the nodal dissection to a D1/D1+ in high-surgical-risk patients, T2 from T3 in order to correctly refer the patient for upfront surgery (T2) or neoadjuvant chemotherapy + surgery (T3) and, finally, T3 from T4a in order to plan a staging laparoscopy/cytological examination of peritoneal washing fluid. Nevertheless, the main message is "to differentiate T2 from T3 cancer", especially if there is no clinical evidence of nodal involvement, since in that scenario a cancer ≥T3 remains the only criterion for directing the patient to neoadjuvant treatment [10, 11]. The reported accuracy of CT in T staging is not optimal, reaching about 82.7% if performed by skilled radiologists, but it is strictly linked to a rigorous CT examination methodology, in particular gaseous/liquid distention and hypotonization of the gastric wall (Table 7.2 and Fig. 7.2), and to meticulous evaluation of CT images through multiplanar reconstruction directly made by radiologists [11]. Imaging semeiotics for the assessment of the T parameter on CT

**Table 7.2** Computed tomography technical parameters

| | |
|---|---|
| Slice thickness | 1.25 mm |
| Beam pitch | 0.9 |
| Reconstruction interval | At least half of the slice thickness |
| Tube voltage (kVp) | 120–140 |
| Reference mAs | Range 200/250–500/600 |

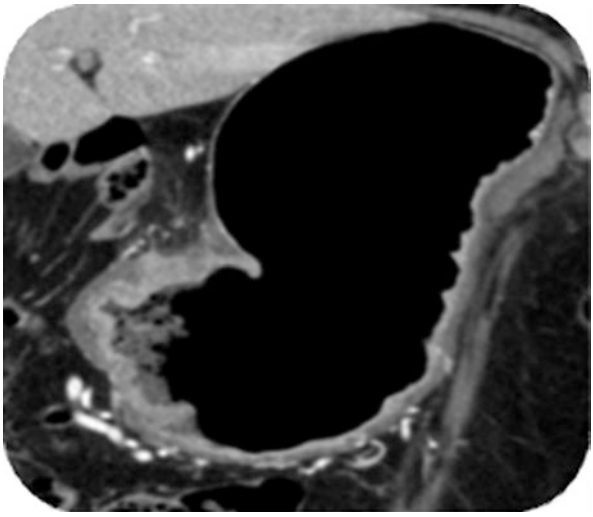

**Fig. 7.2** Air distension of the stomach obtained by administering per os effervescent granules, together with 10 mL of water, immediately before the scan. Table 7.2 shows the correct computed tomography technical parameters

is based on the concepts that only the mucosa appears hypervascular in contrast-enhanced CT whereas the submucosa, muscularis propria, subserosa and serosa together appear as a low-density-stripe (Table 7.3 and Fig. 7.3) [10]. However, not all gastric lesions have the same characteristics of contrast-enhancement (sometimes they are hypovascularized); finally, tumoral infiltration into the gastric walls could be accompanied by inflammatory, edematous or fibrotic changes beneath the cancer, leading to overstaging of the T parameter (Fig. 7.4) [12].

## 7.4 N Staging

If it is not easy to determine the T parameter, imaging could still help in choosing the correct treatment for the patient (neoadjuvant or not), by assessing the N parameter.

Determining the N parameter is fundamental to discriminate N0 and N-positive patients, who will benefit from chemotherapy. It is also relevant to discern N0 from N positive patients, since the N status is one of the most important prognostic indicators in GC. Imaging also has a role in defining which lymph node stations are involved, in order to guide the surgical dissection as also the type of dissection could be customized on the patient [3].

**Table 7.3** Computed tomography criteria for clinical T stages

| Clinical T stage | Computed tomography criteria |
|---|---|
| T1a | Tumor shows enhancement and/or thickening of the inner mucosal layer with intact low-density-stripe layer |
| T1b | Disruption (<50%) of the low-density-stripe layer |
| T2 | Disruption (>50%) of the low-density-stripe layer |
| T3 | No discrimination between the tumor and the outer layer with a smooth outer margin or a few linear strands extending to the perigastric fat |
| T4a | Irregular or nodular outer margin and/or dense perigastric fat infiltration |
| T4b | Obliteration of the fat plane between the tumor and adjacent organs or direct invasion of adjacent organs |

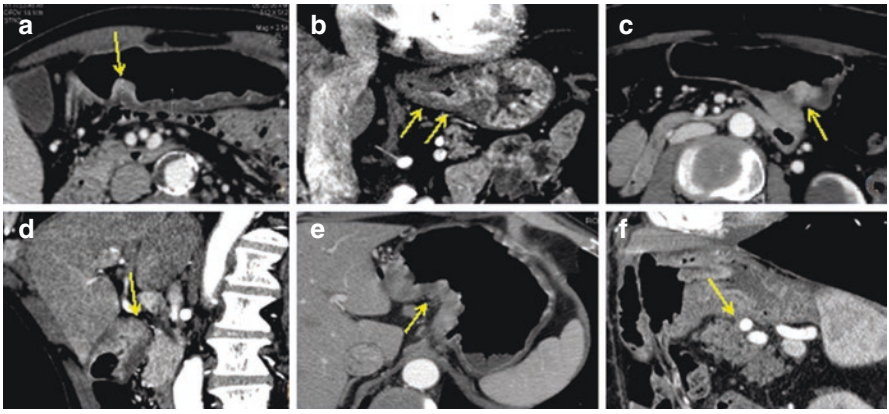


**Fig. 7.3** Computed tomography examples of cT gastric cancer: (**a**) cT1a, (**b**) cT1b, (**c**) cT2, (**d**) cT3, (**e**) cT4a, (**f**) cT4b

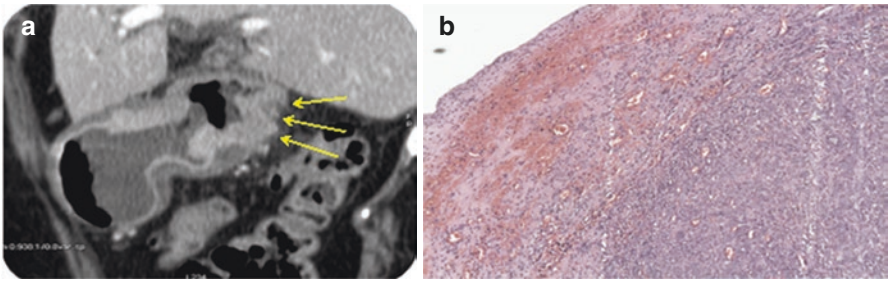


**Fig. 7.4** An example of overstaging of the T parameter after neoadjuvant treatment of a gastric cancer. According to computed tomography (**a**) this was staged as ycT4a, whereas pathology (**b**) revealed a ycT2 due to the presence of fibrosis on the external portion of the lesion (histological image courtesy of Dr. Carla Vindigni)

Regarding the assessment of nodal status in GC in terms of positive or negative, CT is considered to have a limited role and there is no definite method reported in the literature. Various criteria have been investigated, such as single or double size cut-off and morphological characteristics on post-contrast scans [13–15]. Other studies evaluated a cut-off for lymph node maximal area and the sum of the diameters of lymph nodes, reaching an accuracy of about 75–80% [16–18]. At present, the best criterion, also from a practical viewpoint, is the double short-axis cut-off (5 mm for perigastric stations and 8 mm for extraperigastric). PET/CT is highly specific but has limited sensitivity related to non FGD-avid histotypes and the issue of the micrometatasis phenomenon in GC [19]. Recently, extramural venous invasion has been evaluated on CT and seems to be effective for predicting independently node status; moreover, it has a negative prognostic role [20].

To conclude, in recent years, radiomics and texture analysis applied to images have been taking hold for evaluating tumor stage, predicting response to therapy and prognosis, and they probably represent the future of diagnostic imaging in the era of personalized medicine [21–24].

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# The Role of Staging Laparoscopy

8

Leonardo Solaini, Luigi Marano, and Paolo Morgagni

## 8.1 Staging Laparoscopy for Gastric Cancer

The first report on the use of laparoscopy to stage gastric cancer dates back to the 1980s [1]. In this study, Popova et al. found that laparoscopy could have prevented 42.5% of 193 gastric cancer patients from having to undergo unnecessary laparotomy [1].

Nowadays, staging laparoscopy is a recommended step of the preoperative work-up in most of the published guidelines [2–7] (Table 8.1). Its main role is to detect the presence of peritoneal involvement for which computed tomography (CT) scan displayed low accuracies.

For this reason, staging laparoscopy is of vital importance in the assessment of patients with gastric cancer as the presence of peritoneal carcinomatosis would dramatically change the choice of the type of treatment and the expected prognosis.

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**Table 8.1** Guideline recommendations for staging laparoscopy by year of publication

| Source | Year | Recommendation |
|---|---|---|
| European Society of Medical Oncology (ESMO) | 2016 | All patients with resectable gastric cancer |
| Gruppo Italiano Ricerca Cancro Gastrico (GIRCG) | 2017 | Cases deemed to be at risk of peritoneal carcinomatosis not visible or doubtful at CT examination |
| French Intergroup | 2018 | Resectable gastric cancer to exclude peritoneal carcinomatosis or radiologically occult metastatic disease |
| Japanese Gastric Cancer Association | 2018 | Patients with relatively high risk of peritoneal dissemination |
| Spanish Society of Clinical Oncology | 2020 | Resectable gastric cancer with clinical T3 and T4 cancers or in those at higher risk for metastatic disease, such as poorly differentiated cancers and those with a higher nodal burden |
| National Comprehensive Cancer Network (NCCN) | 2020 | Clinical stage T1b or higher |

## 8.2 Technique, Safety and Adjuncts

Staging laparoscopy can be carried out with a three-trocar technique with the patient in supine position with legs apart. The inspection of the abdominal cavity should include the site of the primary tumor, the surrounding peritoneum, liver surface, diaphragm, omentum, small bowel and pelvis. It is debated whether to explore inside the omental bursa or not. A few [8–14] studies reported the inspection of the lesser sac, but they were not comparative studies and a higher accuracy in detecting the right course treatment to follow cannot be proved.

Some advocated that the total length of mesentery must be inspected: two Japanese studies [8, 15] reported that their technique included the exploration of the entire bowel, but, again, it could not be proved that this could increase the rate of peritoneal involvement detection.

Staging laparoscopy is a safe procedure, with most studies reporting 0% morbidity rates. The complication rate ranges from 0% to 3.2% [16], with four studies reporting intestinal injuries [17–20].

In our current practice, we routinely explore the omental bursa and we limit the inspection of the small bowel to those selected cases at high risk of peritoneal carcinomatosis.

Laparoscopic peritoneal lavage for peritoneal cytology is a routine step in staging laparoscopy, as it allows the surgeon to identify microscopic spread in the absence of detectable dissemination. Currently, peritoneal cytology status is an integral part of the TNM staging system. Peritoneal lavage consists of the instillation of 250 mL of physiological saline into the abdominal cavity, which is subsequently aspirated. The lavage fluid can be analyzed by standard cytology or real-time polymerase chain reaction.

At the beginning of the experience with staging laparoscopy, peritoneal cytology seemed not to be useful to complete the staging of gastric cancer [21, 22], conferring little benefit in terms of prognosis [21]. More recently, it has been shown that cytology-positive patients without peritoneal involvement had a significantly better prognosis than those carrying both characteristics [23]. Furthermore, a few studies demonstrated the importance of knowing the peritoneal cytology status [24, 25].

A further adjunct to staging laparoscopy is intraoperative ultrasound, which may be useful to detect deep hepatic lesions. Its use was also recommended in the 2010 Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines on diagnostic laparoscopy [26]. However, the published studies on the topic reported conflicting results, with few supporting the routine use of laparoscopic ultrasound [27, 28] while others could not find any benefits from its application [29–31].

## 8.3 Accuracy and Yield of Staging Laparoscopy

Staging laparoscopy displays a high accuracy in detecting peritoneal carcinomatosis in gastric cancer patients. A recent meta-analysis by Ramos et al. [32], which included five studies for a total of 240 patients, showed that the pooled overall sensitivity was 84.6% (95 CI, 74.7–91.8%), while specificity was 100% (97.7–100%). A recent review reported false negative rates ranging from 0% to 17.2% [16].

However, it must be highlighted that the definition of "false negative" in those studies is related to the finding of peritoneal carcinomatosis or positive peritoneal cytology at the subsequent laparotomy performed with curative intent several weeks after staging laparotomy. In addition, the highest rates of false negative results were found in those series reporting indications for staging laparoscopy for large Bormann type 3 or type 4 or cases suspicious for peritoneal involvement [14, 15, 33].

The yield of staging laparoscopy is defined in most of the reported series as the ratio of patients whose laparoscopy showed clinically important findings over all patients who underwent staging laparoscopy. This could vary from 51.6% to 13.7% depending on the indications for staging laparoscopy adopted in the various studies [15, 17, 20, 33–36]. The yield could be affected by several factors. Nassour et al., analyzing a series of 143 patients, reported a yield of 34%, which was as high as 44% in the Hispanic population. The authors, performing a multivariate analysis, showed that clinical T3/T4 staging, signet ring cells and poorly differentiated tumors could predict radiographically occult disease [37].

Additional data on the role of laparoscopy in staging advanced gastric cancer will be given by the PLASTIC-study [38]. The investigators will try to define the proportion of patients in whom staging laparoscopy and positron emission tomography (PET) scanning could lead to a change in treatment strategy; they hypothesized that the yield of staging laparoscopy and PET will result in a change in treatment strategy in 27% of patients.

## 8.4 Indications

The indications for staging laparoscopy may vary among different countries, but there is a substantial agreement on performing it in those cases of potentially resectable advanced gastric cancer. A few studies tried to find those factors which could have guided the surgeon in performing staging laparoscopy only in a selected group of patients.

Recently, Ikoma et al. [36] found that patients with poorly differentiated cancers, linitis plastica and suspicious CT, were at high risk of peritoneal carcinomatosis at staging laparoscopy. The authors found that, after excluding patients with those characteristics, the rate of peritoneal involvement dropped from 32.1% to 11.2%.

A Japanese prospective analysis [33] on 721 T3–T4 patients verified the diagnostic accuracy of their indication for staging laparoscopy; they included patients with potentially resectable large type 3 tumors with a diameter ≥8 cm and type 4 tumors. The authors found that those characteristics had 67.6%, 76.5%, and 74.3% of sensitivity, specificity, and overall accuracy for peritoneal disease.

Allen et al. [39] analyzed the impact of performing staging laparoscopy even in early stage gastric carcinoma. Interestingly, they found that 17.9% (all poorly differentiated adenocarcinoma) of 56 T1–T2 patients had either gross carcinomatosis and/or positive peritoneal cytology, suggesting the usefulness of this procedure to stage not only advanced cases.

In our current practice, we generally perform staging laparoscopy in all patients who should be treated with perioperative chemotherapy, before starting treatment. However, based on the above-reported evidence, it is considered mandatory in locally advanced tumors with Laurén diffuse tumors (that correspond to poorly cohesive cases according to the WHO and the poorly differentiated non-solid type of the Japanese pathological classification). Of note, without staging laparoscopy it is impossible to have information on peritoneal cytology status, but this would dramatically change the therapeutic pathway of patients who were candidate to perioperative chemotherapy on the bases of clinical staging.

In patients with metastatic disease, staging laparoscopy would allow one to distinguish between “oligometastatic” peritoneal involvement and “highly metastatic” cases that could be potentially eligible for conversion surgery.

It is debated whether to re-perform staging laparoscopy after chemotherapy. This may be useful in those cases which did not show a clear response to chemotherapy or at risk of progression in the context of perioperative treatment. In addition, as reported also by Nakamura et al. [40], it should be a recommended step in cases of metastatic disease in which conversion surgery is planned in order to confirm the regression seen at imaging and verify the peritoneal cytology status after treatment.

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# Part III

# Treatment

# Early Gastric Cancer: Endoscopic Treatment

9

Filippo Catalano and Antonello Trecca

## 9.1 Introduction

The early detection of gastric cancer is now well established all over the world [1]. In Japan, more than 80% of cancers are diagnosed at an early stage, while in the West gastritis-like cancer lesions are still missed during routine endoscopy due to their lower incidence. In the East, most early cancers are treated by endoscopy [2].

The possibility of a less invasive treatment was studied in Japan for three main reasons: clinical, oncological, and technical. The clinical aspect relates to the fact that many elderly patients developed early cancer when they were at high risk of surgical treatment [3, 4]. Gotoda et al. performed a retrospective study on more than 5000 surgically resected early gastric cancers showing that well-differentiated mucosal cancer without lymphovascular involvement had no risk of lymph node metastases, so in these cases endoscopic treatment could be the curative treatment option [3–5]. The history of operative endoscopy started in 1973 when Deyhle et al. performed and reported for the first time a colonic polypectomy [6]. Thereafter, endoscopic techniques underwent continuous development, with more complex and modern upgrades (strip biopsy, Tada 1984; EMR C, Inoue 1993; EMR L, Akiyama 1997). Nevertheless, all these modalities are not enough to carry out an en-bloc resection of the lesion, the only one able to guarantee correct histological evaluation of lateral and vertical margins, degree of differentiation, and lymphovascular infiltration on the resected specimen. Therefore, accurate staging and grading of the lesion can definitively establish whether endoscopic treatment could be considered complete or incomplete from the oncological point of view. In 1999 Gotoda et al.

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first reported in the Japanese literature the use of a specialized insulated-tip (IT) knife and then published the first English-language description of a rectal endoscopic submucosal dissection (ESD) [7]. In the East, ESD quickly gained popularity and became the favored option for the management of early gastric cancer, supported by the well-documented higher en-bloc and curative resection rates and decreased local recurrence [8]. A national registry was created in 2011 among a total of 89 Japanese institutions. It analyzed a total of 3561 patients and compared the results of the two main endoscopic procedures, endoscopic mucosal resection (EMR) and ESD, performed during the year 2004. The en-bloc resection rate and complete resection rate were higher in the ESD group and the incidence of complications was very low in both groups (0.3% in EMR group and 0.4% in ESD group) [8]. In Western countries the lower incidence of the disease and the long learning curve of the ESD procedure with a higher incidence of complications (bleeding, perforation), limited the implementation and spread of this procedure to only a few high-volume gastric cancer centers [9].

EMR is still accepted as a standard of care for the treatment of small gastric lesions as it is easy to perform and needs no specific learning curve. Nevertheless, this technique has two major limitations: resection size is limited by the diameter of the snare, and the margins of the cut are unpredictable, because of slipping of the snare on the target lesion when it is fastened tightly for the resection. Incomplete resections were evident after EMR procedures. The ESD technique was first proposed by Hosokawa and is completed with the IT knife (IT knife 2, Olympus, Tokyo, Japan) [10]. After marking normal mucosa surrounding the lesion at least 5 mm away from the tumor by using a standard needle knife (Olympus, Tokyo, Japan) with a forced 20 W coagulation current (ICC 200 or VIO 200 ERBE Tübingen, Germany), a submucosal injection is obtained with a saline solution mixed with epinephrine (0.04 mg/mL) and a small amount of indigo carmine. A circumferential mucosal incision is started with a needle knife outside the marks in the 60 W endo-cut mode effect 3 and then completed with the IT knife, in the 60–80 W endo-cut mode effect 3 (ICC 200 ERBE, Tübingen, Germany). A submucosal dissection is then obtained with the IT knife underneath the lesion. Hemostasis during the procedure is achieved with the same knife or with hemostatic forceps (Coagrasper, Olympus, Tokyo, Japan) (Fig. 9.1).

## 9.2 Indications

In the 2014 Japanese gastric cancer treatment guidelines, EMR/ESD is indicated as a standard treatment (absolute indication) for differentiated-type adenocarcinoma without ulcerative findings, with T1a depth of invasion and a diameter ≤20 mm [11]. With the last 2018 guidelines (based on retrospective and multicenter studies carried out in Japan) [12], an absolute indication for ESD was introduced also for T1a well-differentiated adenocarcinoma >20 mm if ulcer-negative and ≤30 mm if ulcer-positive. An undifferentiated-type adenocarcinoma (poorly differentiated and signet ring cell according to the Japanese Classification of Gastric Carcinoma;

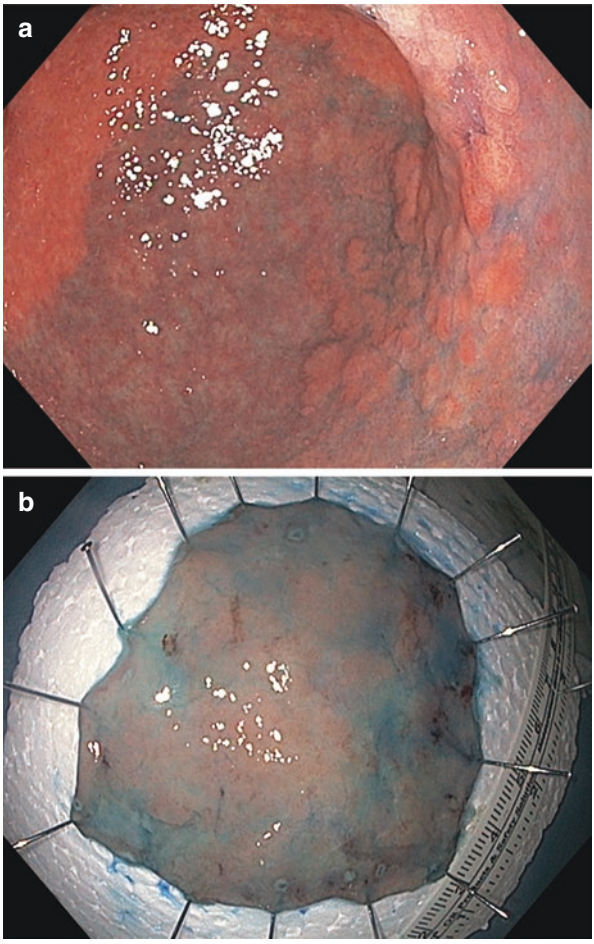


**Fig. 9.1** (**a**) T1a differentiated-type adenocarcinoma without ulcerative findings. (**b**) Endoscopic specimen

tubular G3 and poorly cohesive according to the WHO Classification) without ulcerative findings, with T1a depth of invasion and diameter ≤20 mm is considered in the expanded indication as well as T1b submucosal cancers in the case of invasion <500 μm (sm1) and diameter ≤30 mm, differentiated type, no lymphovascular invasion, negative horizontal and vertical margin (Fig. 9.2; Table 9.1).

The wording "absolute indication" is used in guidelines for tumors with <1% risk of node metastasis and "expanded indication" for tumors with <1% risk of node metastasis but with poor evidence in long-term outcome.

In 2015, the European Society of Gastrointestinal Endoscopy (ESGE) published the ESD Guideline for early neoplastic lesions of the gastrointestinal tract [13]. ESGE recommends endoscopic resection for the treatment of superficial neoplastic lesions that carry a very low risk of lymph node metastasis. EMR is an acceptable option for lesions smaller than 10–15 mm with a very low possibility of advanced histology (Paris 0–IIa). However, ESD is recommended as the treatment of choice

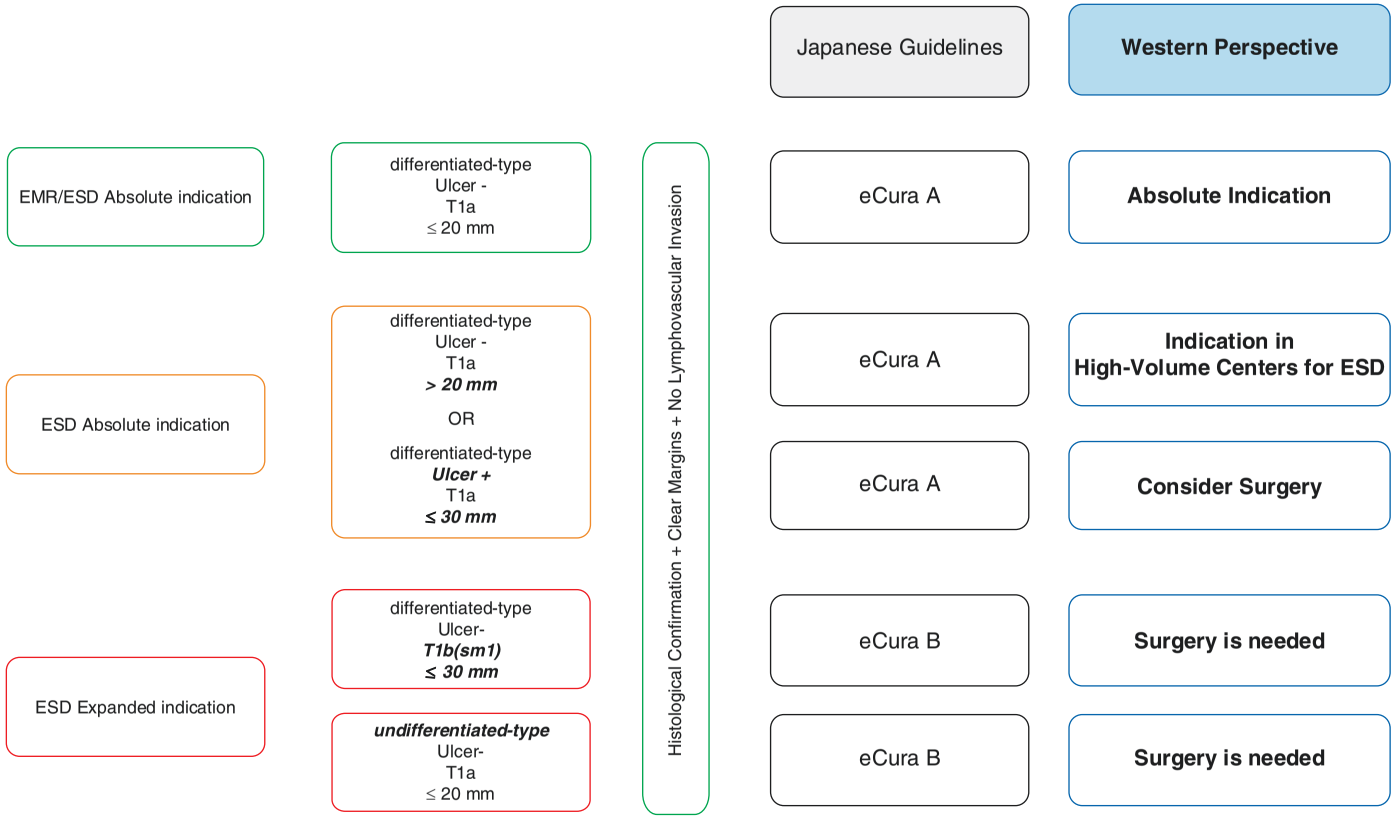


**Fig. 9.2** Indications for endoscopic treatment of early gastric cancer. *EMR* endoscopic mucosal resection, *EMD* endoscopic submucosal dissection

**Table 9.1** Expanded criteria for endoscopic submucosal dissection (ESD) derived from the incidence of lymph node metastases in a large Japanese series

| Criteria | Incidence | 95% CI |
|---|---|---|
| Intramucosal cancer<br>differentiated adenocarcinoma, no lymphatic-vascular invasion, irrespective of ulcer findings, tumor less than 3 cm in size | 0/1230 (0%) | 0–0.3% |
| Intramucosal cancer<br>differentiated adenocarcinoma, no lymphatic-vascular invasion, without ulcer findings, irrespective of tumor size | 0/929 (0%) | 0–0.4% |
| Undifferentiated intramucosal cancer<br>no lymphatic-vascular invasion, without ulcer findings, tumor less than 3 cm in size | 0/141 (0%) | 0–2.6% |
| Minute submucosal penetration (SM1)<br>differentiated adenocarcinoma, no lymphatic-vascular invasion, tumor less than 3 cm in size | 0/145 (0%) | 0–2.5% |

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for most superficial gastric neoplastic lesions, confirming the indications proposed in Japanese guidelines.

## 9.3 Curability

The latest Japanese guidelines introduced a new concept of curability [12]:

- *Endoscopic curability A* (eCuraA), when "absolute indication" is confirmed in the specimen together with clear margins and no lymphovascular invasion.
- *Endoscopic curability B* (eCuraB), in cases of "expanded indication" together with clear margins and no lymphovascular invasion.
- *Endoscopic curability C* (eCuraC): all the other cases in which gastrectomy, in patients fit for surgery, is indicated.

Categories eCuraA and eCuraB differ for the type of follow-up required, which should be more aggressive in eCuraB since reliable long-term data are still lacking.

In Western clinical practice, the gastrointestinal pathologist evaluates the resected specimens cut into thin parallel sections of 2 mm according to the Vienna Classification of epithelial neoplasia [14]. Curative resection is defined when the lateral and vertical margins of the specimens are free of cancer and no lymphatic invasion or vascular involvement are detected. Noncurative resection includes those which do not meet the curative criteria or T1b cancers or when poorly cohesive/signet ring cell or undifferentiated carcinoma is found. In all cases, the degree of cancer differentiation is studied at each cut section. Surgical resection is indicated in the case of noncurative resections as well as in cases of "expanded indication" which should be considered investigational and applied in controlled prospective trials.

## 9.4 Results of Endoscopic Submucosal Dissection

The major advantage of ESD is the higher rate of en-bloc resection compared to EMR, especially in large lesions (90–92%), improving the correct pathological evaluation [15] with a curative resection rate around 93% [16]. Multicenter clinical trials have also shown that ESD has lower rates of local residual tumor and recurrence than EMR [17]. Complications of ESD are bleeding and perforation, in the majority of cases treated by endoscopy. In selected cases, surgical treatment could be useful for the treatment of perforation.

The Western experience is confined to a few centers with a limited number of endoscopists, resulting in highly variable outcomes, with R0 resection rates of 37–100%, en-bloc resection rates of 53–100%, a mean procedure time of 74′–176′, and complication rates of 5–50%, depending on operator experience [18–25]. Early diagnosis is still difficult due to the low frequency and limited experience in endoscopic evaluation of the minimal mucosal changes of the disease. The level of evidence of ESD is so far based on data from Japan. It remains undetermined whether these results can be applied to Western countries, owing to the lack of appropriate trials [26]. The Asian experience seems difficult to implement in the West. The ESD technique has been sufficiently implemented in the reference centers but accurate organization of the data is still lacking. If we consider that ESD treatment is primarily a diagnostic procedure, the pathological evaluation should be standardized and shared in order to avoid the loss of important criteria for assessing curability. Appropriate data sharing between the endoscopist and pathologist and trustworthy long-term results are unfortunately still missing in the Western world.

## 9.5 Conclusions

To summarize, also in agreement with the latest version of the Japanese guidelines, there are two types of absolute indication for endoscopic resection: absolute indication for EMR/ESD and absolute indication for ESD.

The absolute indication for EMR/ESD, which should also be applied in Western settings, comprises T1a well-differentiated adenocarcinomas that are ulcer-negative and $\leq$20 mm in size.

Conversely, the absolute indication for ESD includes T1a well-differentiated adenocarcinomas that are either ulcer-negative and >20 mm in size or ulcer-positive and $\leq$30 mm in size. In these cases, in Western settings the ESD procedures should be centralized and performed by endoscopists with specific experience given that the critical aspects of this indication (size and ulceration) are technical rather than oncological. (Fig. 9.2).

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# Surgical Approaches in Early Gastric Cancer: Open and Minimally Invasive

# 10

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Gastrectomy remains the treatment of choice for patients with early gastric cancer that are not suitable for endoscopic treatment or in the case of non-curative endoscopic resections. Over the last decade, laparoscopic gastrectomy has gradually gained popularity as a surgical option for distal early gastric cancer, especially in Eastern countries, with most of the evidence coming from Korea and Japan.

## 10.1 Laparoscopic Distal Gastrectomy

Two recent large-scale phase III randomized clinical trials investigated the surgical safety of laparoscopic-assisted distal gastrectomy (LADG) compared with open distal gastrectomy (ODG) in patients with stage I distal gastric cancer in a highly selected population [1, 2].

The KLASS-01 (Korean Laparoscopic Gastrointestinal Surgery Study) multicenter trial—involving 1416 patients from 13 different Korean institutes and including 15 experienced surgeons—showed a significantly lower incidence of postoperative surgical complications in the laparoscopy group compared to open surgery (13.7% vs. 18.9%, respectively).

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When analyzing more in detail the type of complications, the only one that showed a statistically significant difference was wound infections, with 3.6% in the laparoscopic arm and 7.0% in the open surgery group. This evidence and the lower surgical stress associated with laparoscopy are likely the main causes of the reduced length of stay of almost one day in laparoscopically treated patients (LADG 7.1 ± 3.1 vs. ODG 7.9 ± 4.1, $p < 0.001$).

LADG compared to ODG showed a reduced estimated blood loss but a higher intervention time. However, in the LADG group, a lower rate of D2 lymphadenectomy was performed (56.0% vs. 64.2% in ODG, $p = 0.003$) with fewer lymph nodes harvested. These results may reflect a less aggressive attitude in minimally invasive surgery and therefore better short-term outcomes. Regarding mortality and re-intervention rate, no differences were demonstrated between the two surgical approaches [1].

One year later, the Japan Clinical Oncology Group randomized trial (JCOG0912) substantially confirmed the results of the Korean group. Specifically, 921 patients from 33 institutions were enrolled and randomly assigned to receive ODG or LADG. Japanese surgeons demonstrated the non-inferiority of LADG compared to ODG in terms of mortality and complication rates (3.3% and 3.7%, respectively), confirming the advantage in favor of the laparoscopic group in terms of lower estimated blood loss and shorter hospital stay. Unlike the KLASS-01, the Japanese trial showed no advantage in favor of the laparoscopic arm in terms of wound complications. Conversely, they found a higher proportion of patients with grade 3–4 elevation of ALT/AST in the LADG group, which is probably explained by the constant hepatic retraction during the whole duration of the laparoscopic surgery, which also appears to be longer (LADG 278 min vs. ODG 194 min, $p < 0.001$), associated with the influence of pneumoperitoneum in reducing portal venous circulation. Unlike the Korean trial, the Japanese trial found a comparable percentage of D2 lymphadenectomies in the two arms [2].

Recently, the long-term oncological results of these two large-scale multicenter randomized controlled trials were published [3, 4]. The KLASS-01 trial showed that there are no significant differences in terms of overall survival (94.2% in the LADG group and 93.3% in the ODG group, $p = 0.64$) and cancer-specific survival (97.1% in the LADG arm and 97.2% in the ODG arm, $p = 0.91$) after five years of follow-up [3]. Similar results are reported by Japanese authors [4], demonstrating the non-inferiority of LADG over ODG when performed by experienced surgeons.

One concern would be the high selection of patients in these Korean and Japanese trials. Indeed, elderly patients over the age of 80, obese patients as well as patients with severe comorbidities or with a previous history of upper abdominal surgery were excluded. In order to answer this question, Fujiya et al. compared through a propensity score matching analysis, patients who underwent ODG and LADG for clinical stage I gastric cancer and who did not meet the above-mentioned inclusion criteria of JCOG0912. The incidence of grade ≥2 postoperative complications according to Clavien-Dindo did not significantly differ between the laparoscopic and laparotomic groups (23.7% vs. 18.6%, respectively, $p = 0.0653$); this was also confirmed by analyzing for each type of complication [5]. These findings seem to support the safety of LAGD in real-life conditions.

Based on this strong evidence, LADG proved to be a safe alternative to open surgery for stage I distal gastric cancer when performed by experienced surgeons.

## 10.2 Laparoscopic Total Gastrectomy

The results obtained with LADG for stage I distal cancer gave impetus to laparoscopic-assisted total gastrectomy (LATG) for more proximal tumors in stage I gastric cancer. LATG is a technically demanding procedure with unsolved safety issues and difficulties being accepted, even in Eastern countries. Indeed, in a retrospective study by Kodera et al., data from 11,740 clinical stage I gastric cancer patients were collected, 7793 of whom underwent open surgery and 3974 laparoscopic surgery. A propensity score matched analysis was performed between the two groups. Of note, the incidence of anastomotic leakage reached a significant difference, being lower in open surgery regardless of leak site (3.6% in OTG versus 5.4% in LATG, $p < 0.001$). Moreover, although the length of hospital stay was significantly longer in the open surgery group, the incidence of readmission and reoperation within 30 days after surgery was higher in the laparoscopic arm (2.7% vs. 1.7% for readmission, $p = 0.002$, and 4.5% vs. 3.3% for reoperation, $p = 0.009$) [6]. These retrospective results raise some doubts about surgical safety in an unselected population.

In a more selected population, as that of KLASS-03, a single-arm prospective multicenter phase II study including 160 patients undergoing LATG, the complication rate was 20.6%, which is comparable to historical controls, 15 patients (9.4%) exhibited grade III or higher complications according to the Clavien-Dindo classification, and anastomotic leakage was present in only three patients (1.9%) [7]. The authors investigated whether the anastomotic technique of esophagojejunal anastomoses (45 extracorporeal circular stapled, 64 intracorporeal circular stapled, and 51 intracorporeal linear stapled anastomosis) impacts the incidence of postoperative complications. Early postoperative complications were similar between groups but long-term complications, specifically esophagojejunostomy stenoses were significantly more frequent in the intracorporeal circular stapling group [8].

Taking together the evidence from the Japanese survey and trial, LATG is still associated with esophagojejunal anastomosis issues such as leakages or stenosis, and these findings should be considered when planning the surgical strategy.

The CLASS (Chinese Laparoscopic Gastrointestinal Surgery Study) group has recently initiated a multicenter randomized controlled trial to compare the short- and long-term outcomes of OTG and LATG, which will solve questions about the surgical and oncological safety of this procedure, when performed by experienced surgeons [9].

## 10.3 Function-Preserving Gastric Resection and Laparoscopic Sentinel Node Navigation

In consideration of the excellent prognosis of patients with EGC undergoing gastrectomy, surgeons in Eastern countries developed surgical function-preserving gastric resections in order to reduce the overall impact of a gastrectomy. These surgical procedures are represented mainly by pylorus-preserving gastrectomy (PPG) and proximal gastrectomy with double tract reconstruction (PG-DT). Currently, the only evidence available in the literature in relation to gastric-preserving surgery is represented by retrospective studies [10, 11].

The theoretical advantage of PPG for EGC located at the middle third is inherent in the surgical technique, which provides, on the one hand, preservation of the pylorus, with a consequent reduction of dumping syndrome, bile reflux gastroesophagitis, weight loss, and nutritional deficiency, and, on the other, preservation of the hepatic branch of the vagus nerve, which reduces gallbladder dysfunction and gallstone sequelae [12]. However, this leads to the risk of inadequate lymph node retrieval, in particular at lymph node stations 5 and 6. A study by Kong et al. highlighted how lymph node metastases in these stations are very rare in middle-third EGC [13]. Moreover, the oncological safety of the PPG procedure has been proved for T1N0 gastric cancer in the middle portion of the stomach in a large retrospective study [11]. Indeed, the main risk of this procedure is underestimation of the clinical stage, which may cause undertreatment of the patients. Important evidence on this topic will be provided by the ongoing KLASS 04 trial (NCT02595086).

For EGC of the proximal stomach, a proximal gastrectomy with PG-DT is thought to improve the patient's quality of life, basically as a result of preservation of the distal stomach and duodenal transit, which reduces vitamin B12 and iron deficiency [14]. The KLASS 05 trial (NCT02892643) is currently investigating the outcomes of laparoscopic PG with double tract reconstruction compared to LATG in patients with upper-third EGC.

Even less invasive approaches compared to PPG and PG have been hypothesized in EGC <3 cm: recently, the short-term outcomes of a multicenter phase III trial (Sentinel Node Oriented Tailored Approach, SENORITA) showed that patients treated with laparoscopic sentinel node navigation surgery (LSNNS), compared with laparoscopic standard gastrectomy (LSG), had similar short-term outcomes [15]. The long-term results (primary endpoints) in terms of oncological safety and quality of life are not yet available.

Although the development of these conservative surgical approaches is an urgent need in Korea and Japan, these are far from becoming part of clinical practice in the West, where the majority of newly diagnosed gastric cancers are at advanced stages.

## 10.4 The Western Point of View

There is very limited evidence on the role of laparoscopic gastrectomy in the treatment of EGC in the West (Table 10.1). As a result, the current surgical indication for minimally invasive gastrectomy in stage I GC is based on the above-mentioned Eastern studies. However, the applicability of randomized trial results in Western clinical practice remains a matter of debate. This dilemma is primarily related to the huge difference in the number of cases in terms of both the global and relative incidence of EGC, but also, in many European countries, to the lack of centralization of the patients, which inevitably has a negative impact on the surgeon's learning curve. On the issue of the learning curve, Eastern authors clearly demonstrated that the risk of postoperative complications was independently associated with the surgeons' expertise, 50 laparoscopic gastrectomies being the cut-off that dramatically improves postoperative outcomes [39–42]. This criticism is even greater with regard

**Table 10.1** Evidence on the role of laparoscopic gastrectomy in the treatment of early gastric cancer in the West

| Study | Publication year | Type of study | OG–LG n. | LTG–LDG n. (%) | pSTAGE I in LG n. (%) |
|---|---|---|---|---|---|
| Huscher et al. [16] | 2004 | R | 0–44 | 8 (18)–36 (82) | 20 (45) |
| Dulucq et al. [17] | 2005 | P | 28–24 | 8 (33)–14 (58)[a] | 11 (45) |
| Huscher et al. [18] | 2005 | RCT | 29–30 | 0 (0)–30 (100) | 13 (43) |
| Varela et al. [19] | 2006 | R | 21–15 | 2 (13)–6 (40)[a] | 9 (60) |
| Pugliese et al. [20] | 2006 | R | 99–48 | 5 (10)–43 (90) | 41 (85) |
| Topal et al. [21] | 2007 | R | 22–38 | 38 (100)–0 (0) | 17 (45) |
| Sarela et al. [22] | 2008 | R | 11–28 | 6 (21)–12 (43)[a] | NA |
| Strong et al. [23] | 2009 | CC | 30–30 | 0 (0)–30 (100) | 18 (60) |
| Bracale et al. [24] | 2010 | R | 0–67 | 56 (84)–0 (0)[a] | 35 (52) |
| Chouillard et al. [25] | 2010 | R | 79–51 | 14 (27)–37 (73) | 18 (35) |
| Orsenigo et al. [26] | 2010 | R | 269–109 | 17 (16)–92 (84) | 54 (50) |
| Sica et al. [27] | 2011 | P | 25–22 | 5 (23)–17 (77) | 2 (9) |
| MacLellan et al. [28] | 2011 | R | 182–21 | NA | 0 (0) |
| Bouras et al. [29] | 2011 | R | 95–259 | 0 (0)–259 (100) | NA |
| Scatizzi et al. [30] | 2011 | R | 30–30 | 0 (0)–30 (100) | 0 (0) |
| Siani et al. [31] | 2012 | P | 25–25 | 25 (100)–0 (0) | 6 (24) |
| Corcione et al. [32] | 2013 | R | 0–92 | 88 (95)–0 (0)[a] | 29 (32) |
| Cianchi et al. [33] | 2013 | R | 41–41 | 29 (71)–12 (29) | 12 (29) |
| Mamidanna et al. [34] | 2013 | R | 10,233–480 | NA | NA |
| Tuttle et al. [35] | 2015 | R | 0–28 | 12 (43)–14 (50)[a] | 1 (4) |
| Kelly et al. [36] | 2015 | R | 87–87 | 26 (31)–60 (69) | 49 (56) |
| Brenkman et al. [37] | 2017 | R | 1663–277 | 137 (49)–140 (51) | NA |
| van der Wielen et al. [38] | 2020 | RCT | 49–47 | 47 (100)–0 (0) | 0 (0) |

*R* retrospective, *RCT* randomized controlled trial, *P* prospective non-randomized, *CC* case-control, *OG* open gastrectomy, *LG* laparoscopic gastrectomy, *LTG* laparoscopic total gastrectomy, *LDG* laparoscopic distal gastrectomy, *NA* not available

[a]Atypical resections not counted

to LATG, in consideration of the technical challenge of performing esophagojejunal anastomoses, as witnessed in the Japanese survey [6].

Another topic of interest for Western surgeons is how body mass index (BMI) impacts the clinical and oncological outcomes in patients undergoing laparoscopic gastrectomy for gastric cancer. Interestingly, in the LADG arm of the JCOG 0912 study, the proportion of surgical complications increased with increasing BMI ($p = 0.012$); on the contrary, this did not happen in the ODG arm ($p = 0.066$) [2]. This evidence is not confirmed by other two studies [39, 40], but in both of these reports the cut-off used to discriminate obese from non-obese patients is 25 kg/m$^2$. The choice of this value, which according to the WHO defines overweight and not obese patients, could obscure the real impact of BMI in LADG. With regard to the long-term outcomes, Katai et al., in the JCOG0912 trial, underline that patients with BMI ≥25 kg/m$^2$ have a tendency to have worse survivals in the laparoscopic group than in the laparotomy group (HR 1.72, 0.56–5.25) [4]. This could be at least partially due to a lower number of retrieved lymph nodes in patients with high BMI compared to those with low BMI, as reported by Korean authors [43].

It should be noted that a low rate of D2 lymphadenectomies were performed in the two Eastern trials [1, 2], in accordance with the Japanese guidelines on gastric cancer. However, a recent European audit has shown that experienced surgeons modulate the extent of lymphadenectomy according to the tumor and patient characteristics, preferring D2 lymphadenectomies in patients with more aggressive forms of EGC, such as those with diffuse histotypes according to Laurén [44]. This should be taken into account when planning a laparoscopic gastrectomy for EGC in the West.

In conclusion, LADG seems to be comparable to ODG in terms of surgical and oncological safety. The evidence from Korea and Japan on this topic can be roughly transposed to high volume Western centers, paying attention to some subgroups of patients such as obese patients.

LATG has proven to be a complex procedure that can be particularly demanding due to the technical issue of esophagojejunal anastomosis, so concerns still exist regarding the surgical safety of the procedure.

## 10.5 Robotic Surgery

Robotic gastrectomy (RG) was introduced with the aim of overcoming some disadvantages of standard minimally invasive surgery such as the lack of three-dimensional and magnification views of the operating field, involuntary tremor, and straight forceps that do not allow great freedom of movement.

Currently, robotic surgery is not reported by the international guidelines as a standard for the treatment of gastric cancer. This is due to a lack of evidence supporting robotic surgery in this setting, given that the studies available so far are mostly retrospective studies with small cohorts of patients. Meta-analyses have shown no clear advantages of robotic surgery over laparoscopic surgery in terms of both short- and long-term outcomes [45, 46].

A single-arm prospective study by Uyama et al. found a better morbidity rate (Clavien-Dindo grade ≥IIIa) in 330 patients who underwent RG compared with historical controls (laparoscopic gastrectomy) (2.45% RG vs. 6.4% laparoscopic gastrectomy, $p = 0.0018$). Notwithstanding the limits of such a comparison, RG was approved for national medical insurance coverage in Japan after publication of this study [47].

Unlike the above-mentioned Japanese paper, the prospective multicenter comparative study conducted by Kim et al. demonstrated how, in spite of an increase in costs and operation time, no significant improvements were observed in estimated blood loss, rates of open conversion and postoperative outcomes with the robotic compared to the laparoscopic approach [48].

Phase III randomized controlled trials are awaited that will provide us with more evidence on this topic and clarify the role of this type of surgery in patients with gastric cancer [49].

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# Locally Advanced Gastric Cancer: Neoadjuvant Treatment

# 11

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## 11.1 Introduction

The 5-year survival rate for resectable stage II and III gastric cancer (GC) is approximately 20–30% in the Western world, while it is approximately 70% in Eastern countries [1]. GC is a complex disease for which it is important to have an accurate clinical staging and the integration of biological/molecular knowledge for the definition of the treatment.

Over the years there has been an increasing attention to multidisciplinary patient management with extensive use of neoadjuvant or perioperative chemotherapy, now considered the standard of care in operable GC. This therapeutic management has improved clinical outcome, in particular long-term prognosis and disease-free survival (DFS), and had positive impact on overall survival (OS) in patients with gastric disease at stage II and III.

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The objectives of these treatments are to eliminate micrometastases and obtain downstaging of disease with an increase in the rate of surgical resections without residual disease (R0).

The anticipation of chemotherapy makes it possible to treat patients in better clinical condition; furthermore, the disease has an optimal vascularization and so we can also test chemotherapy sensitivity. Obviously, treatment resistance with progression of disease is possible. For this reason, it is important to discuss the cases in a multidisciplinary approach.

Currently the guidelines of the National Comprehensive Cancer Network (NCCN) [2] and Associazione Italiana Oncologia Medica (AIOM) [3] recommend preoperative chemotherapy for operable GC with clinical stage ≥T2 or N+, while the European Society for Medical Oncology (ESMO) [4] suggest perioperative chemotherapy for patients with stage ≥IB resectable GC.

## 11.2 Current Status of Studies

The first perioperative therapy study was published in 2006 and documented an absolute 13% increase in OS and a 9% increase in the radical surgery rate (R0) using anthracyclines containing perioperative chemotherapy (ECF: epirubicin, cisplatin and fluorouracil) compared to surgery alone [5].

Subsequently, in 2011 the FNCLCC-FFCD French study was published that confirmed the improvement obtained by fluoropyrimidine and platinum perioperative chemotherapy, reporting a 10% increase in the R0 rate and a 14% increase in 5-year OS [6].

More recently, in 2017, Al Batran reported an absolute increase in OS of 22% with FLOT (fluorouracil, oxaliplatin and docetaxel) over anthracycline based chemotherapy [7].

The survival benefit and the interesting complete pathological response rate (15.6%) obtained by FLOT elevates the FLOT regimen to the gold standard for perioperative treatment; nevertheless, we have to consider that less than half of the patients (46%) completed all the allocated cycles [8]. The most common reasons for discontinuing chemotherapy were disease progression, lack of efficacy, early death or chemotherapy toxicities. Another possibility for not completing the treatment could be sarcopenia and sarcopenic obesity [9]. So pre- and postoperative treatment might need to be more individualized.

Another unresolved question is the role of postoperative chemotherapy after neoadjuvant therapy or in perioperative settings, for which no definitive data exist.

The Japanese Gastric Cancer Association [10] suggested S-1 [11] or Xelox (oxaliplatin plus capecitabine) adjuvant chemotherapy to be effective [12], while studies conducted in Asiatic countries did not have comforting results in neoadjuvant settings.

Furthermore, the applicability of Asiatic data to the Caucasian population is still a reason of debate.

Currently, we are waiting for the results of the PRODIGY8 study which is evaluating the addition of taxane-based triplet in neoadjuvant setting [13].

A recent network meta-analysis confirmed that taxane-based perioperative chemotherapy was more effective than surgery alone (HR 0.58) and performed better than adjuvant chemotherapy (HR 0.62) [14].

All studies conducted up to now have demonstrated a superiority of preoperative chemotherapy compared to surgery alone, followed or not by adjuvant chemotherapy. However, we have no conclusive results regarding the comparison between perioperative and neoadjuvant treatments [15] and no clear data exist that indicate the best regimen to use.

The GASTRODOC was a randomized, open-label, phase-II trial study published in 2020 [16] which sought to verify, as primary endpoint, if neoadjuvant treatment was superior to perioperative therapy in terms of the percentage of completed cycles of chemotherapy in patients with operable gastric cancer. The study used the same taxane-based treatment regimen: DOC (docetaxel, oxaliplatin and capecitabine) both in the neoadjuvant regimen (4 cycles pre surgery) and in the perioperative regimen (2 cycles pre and 2 cycles post surgery). Stage II and III gastric cancer patients were enrolled. Compared to other perioperative studies, it did not include early stages of disease (early gastric cancer) or extragastric localization of disease (distal esophagus or cardias). Laparoscopy was always performed, even when carcinosis was not suspected at the diagnostic computerized tomography scan: peritoneal positive cytology patients were excluded. The cancer centers participating in the trial were required to have their patients operated by Italian Research Group for Gastric Cancer (GIRCG) surgeons. This study reported that the neoadjuvant approach with four cycles was more frequently completed and more active than the perioperative approach, although the number of patients who completed the treatment did not significantly differ between arms.

If we consider the duration of neoadjuvant treatment, we know that two months of therapy are adequate on the basis of an extrapolation from the MAGIC and FNCLCC-FFCD trials and of the results from UK MRC OE05 [17], in which four cycles of neoadjuvant ECX (epirubicin, cisplatin, and capecitabine) compared with two cycles of CF (cisplatin and fluorouracil) did not increase survival.

If we consider the perioperative studies (MAGIC and FNCLCC-FFCD), the 5-year OS in the preoperative chemotherapy arms was always lower than that reported in the Western and in the Eastern experiences, in which D2 lymphadenectomy surgery was performed followed by adjuvant chemotherapy. This could be partly explained by heterogeneity in the patients' characteristics: for example, there were 11% of gastroesophageal junction (GEJ) carcinomas in the MAGIC study versus 64% of GEJ cancers in FNCLCC-FFCD. Also the type of surgery was different, with only 40% of D2 surgery in the MAGIC study. A further explanation could be the different molecular and histological characteristics of the diseases considered.

Regarding locally advanced operable GEJ carcinoma, both perioperative chemotherapy and preoperative chemoradiotherapy are valid options. A systematic review and meta-analysis comparing neoadjuvant chemoradiotherapy versus chemotherapy for adenocarcinoma of GEJ found no difference in terms of median OS, despite

a higher pathological complete response rate and a reduced risk of locoregional recurrences being obtained with the combined approach [18].

The ESOPEC trial [19] will compare perioperative FLOT chemotherapy with neoadjuvant chemoradiation according to the CROSS protocol (carboplatin plus paclitaxel and radiotherapy) in multimodal treatment of resectable esophagus/GEJ adenocarcinoma. The goal of the trial will be to identify the superior protocol with regard to patient survival, treatment morbidity and quality of life.

The benefit of the addition of preoperative radiotherapy to perioperative chemotherapy is also currently being evaluated in a phase 3 trial (TOPGEAR) [20].

Several studies have been conducted to evaluate the combination of chemotherapy with panitumumab [21] or bevacizumab [22] in the preoperative setting but the results were always negative. Other combination strategies are currently being evaluated in ongoing studies in resectable GC: immunotherapy combined with chemotherapy (KEYNOTE-585 study [23]), ramucirumab in combination with FLOT [24], trastuzumab and pertuzumab combined with FLOT chemotherapy in HER2 positive GC (PETRARCA study [25]).

We hope that these studies will soon clarify the best strategy.

Important studies have confirmed a significant and independent association between DFS/OS in patients and microsatellite instability (MSI) of the disease. The condition of MSI reflects approximately 10% of operable GC. Post-hoc analysis of MAGIC and CLASSIC [26] found that MSI is a positive prognostic factor in operated patients (3-year DFS increased by 30% and 5-year OS was also increased) but the use of perioperative or adjuvant chemotherapy in MSI patients could be useless or potentially detrimental (result confirmed also in the analysis of the CRITICS study) [27]. In fact, in the MAGIC analysis, MSI patients performed very well with surgery alone and had worse survival when neoadjuvant chemotherapy before surgery was added [26, 28]. Similarly, the 2019 meta-analysis confirmed that MSS patients benefit from chemotherapy added to surgery, with 5-year DFS of 57% (versus 41% with surgery alone) and 5-year OS of 62% (versus 53% with surgery alone) [28].

Finally, the signet ring cell histotype has a controversial benefit over neoadjuvant therapy, with no apparent survival benefit and no increase in the surgical R0 rate after preoperative chemotherapy [29].

## 11.3 Conclusion

In conclusion, it may be reasonable to use fluoropyrimidine–platinum doublet or triplet schedule before surgery, although the strongest evidence is for FLOT combinations. Recommended preoperative treatment duration is about 2 months. The pretreatment evaluation should consider a stage II and III GC. MSI analysis is mandatory already from the diagnosis to guide the definitive therapeutic decision (chemotherapy versus no chemotherapy in both neoadjuvant and adjuvant settings) and optimize the clinical outcome.

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# Resection Margins in Gastric Cancer

# 12

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## 12.1 Incidence of Resection Line Involvement

Resection line involvement (RLI) in advanced gastric cancer is recognized as a significant negative prognostic factor. Only few studies showed that RLI is not an independent prognostic factor, but in such studies RLI was found in the context of gastric cancers diagnosed at a very advanced stage, or in association with macroscopic residual disease at other sites (R2) after surgery [1].

Patients presenting microscopic margin as the only residual cancer site (R1) have been reported in 0.1–1.8% of gastric resections [2] in Eastern studies, in 6.2% in a Dutch study from the Dutch Upper Gastrointestinal Audit [3], in 5.7% at the Memorial Sloan Kettering Cancer Centre [4], and in 11.2% in a study from the American National Cancer Database [5]. This difference is related to the experience of the center, the routine use of frozen section, or the relative proportion of early and advanced cancers considered in the different studies.

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## 12.2 Risk Factors for Resection Line Involvement

Several risk factors for RLI have been observed and are generally related to a specific cancer stage. Bissolati et al. showed that in locally advanced cancer, the risk factors for RLI presented some differences in relation to Laurén's histologic subtypes [6]:

- *T2–T4 cancers with intestinal histotype* risk factors were:
- 1. serosa invasion; 2. esophagogastric junction (EGJ) location; 3. margin distance <3 cm.
- *T2–T4 diffused/mixed pattern histotype* risk factors were:
- 1. lymphatic infiltration; 2. tumor diameter >4 cm; 3. EGJ location; 4. serosa invasion.

A population-based study from the Netherlands studied the relationship between the incidence of positive margins and hospital volume and reported a higher incidence of RLI in patients operated on in centers with a hospital volume <20 resections/year [3].

Considering all the reported risk factors, score systems have been proposed in order to avoid RLI. A recent retrospective study on 2757 patients reported cases of RLI associated with the presence of one or more of the following features: remnant gastric cancer, esophageal invasion, tumor size >80 mm, undifferentiated tumor, macroscopic type IV, pT4 stage. On risk stratification analysis, the incidence of a positive resection line was 0.1% in patients with no risk factor, 0.4% in those with one risk factor, 3.1% with two risk factors, 5.3% with three risk factors, 21.3% with four risk factors, and 85.7% with five risk factors [2].

## 12.3 Resection Line Involvement Guidelines

With specific regard to proximal resection margins, the optimal length from the cranial margin of the tumor to be respected in order to avoid proximal RLI varies among the different international guidelines (Table 12.1) [7–13]. The Japanese

**Table 12.1** National guidelines on resection margins

| National guidelines | Indication |
|---|---|
| UK, 2011 [7] | Ex vivo 3.5 cm |
| France, 2018 [8] | 5 cm, 8 cm if signet ring cells |
| Germany, 2011 [9] | 5 cm if intestinal Lauren's histologic type, 8 cm if diffuse |
| Japan, 2018 [10] | 3 cm for T2/expansive cancer and 5 cm for T3/4 or infiltrating cancer |
| ESMO, 2016 [11] | 5 cm, 8 cm if diffuse type |
| Italy, 2014 [12] | 3 cm for T2/intestinal/expansive cancer and 5 cm for T3/4 or infiltrating cancer |
| NCCN, 2015 [13] | 4 cm for T1/T3 |

guidelines report a 3-cm or 5-cm margin length for differentiated and undifferentiated tumors, respectively [10]. The Italian guidelines substantially overlap with the Japanese as regards the indication of safe proximal resection margins [12]. Of note the German guidelines were the first to recommend wider resection margins, 5 cm for intestinal and 8 cm for diffuse gastric cancer [9].

## 12.4 Frozen Section Procedure

The frozen section procedure is required when it is not possible to obtain a proximal resection margin as recommended by guidelines or in the presence of the risk factors for RLI reported above.

Accuracy of a frozen section is high and reported to be more than 95%. Mc Auliffe et al., considering 3171 frozen section examinations, presented an accuracy of 98.1, with 1.7% false negative results. However, this study also observed that, if cases of signet ring cells and poorly cohesive carcinoma are considered, the false negative rate rises to 2.6% [4].

Signet ring cells and poorly cohesive cancer are often found with inflammatory cells, making the identification of cancer cells more difficult. Rapid immunohistochemical analysis may help in diagnosis, but it is not available everywhere.

A particular subset of patients are those who regressed after neoadjuvant treatment. These patients could be a problem when a previous accurate endoscopy is not available. If the total resection has not been performed, a relapse on the remnant stomach may be observed even if the margins were negative.

## 12.5 Treatment of Proximal Resection Line Involvement

The optimal treatment for patients with proximal RLI after surgery, without evidence of other microscopic/macroscopic residual disease, is debated. Indeed, randomized trials are not feasible in such conditions, allowing different approaches to be proposed on the basis of general oncological concepts.

The indication for reoperation for RLI in the case of locally advanced gastric cancer should be considered when tumor extension is limited, specifically in cases with limited nodal involvement. In cases of RLI, Cascinu et al. suggested surgical reoperation only in patients with pN0 stage disease because only in this group did RLI affect prognosis [14]. Kim et al. demonstrated that a positive resection margin was an independent prognostic factor for patients with less than five positive nodes and, in this group of patients, reoperation improved overall survival [15].

In more advanced disease, with extensive nodal metastases, a higher and early occurrence of distant metastases rather than local recurrence is expected, reducing the impact of a reoperation due to RLI on long-term prognosis [16].

Although the RLI in early gastric cancer is beyond the scope of this chapter, we would like to briefly comment on it. In this setting, different options have been suggested: some studies did not observe any relapses or lower survival rates in these

patients and therefore no re-resection was suggested [17, 18]; other authors, by contrast, do recommend re-resection, especially in those patients where an R0 resection can be achieved [15]. Probably, a careful balancing between surgical risks and oncological benefits must be considered before subjecting these patients to an additional resection.

In conclusion, in cases of proximal RLI after subtotal gastrectomy in patients with a subserosal tumor (pT2-3) and limited nodal involvement (pN0-1), with negative peritoneal cytology, a surgical reoperation is indicated. When the pathological stage of tumor is more advanced, a re-resection is not indicated as the long-term prognosis would likely not be affected by the RLI.

In RLI after total gastrectomy, even in cases of limited disease burden (pT2-3, pN0-1), the indications to perform additional resections that may require a transthoracic approach should be discussed by multidisciplinary tumor board.

Future evidence is awaited, particularly in patients treated with multimodal treatment in whom systemic control of disease may open different clinical scenarios.

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# Locally Advanced Gastric Cancer: Extent of Lymphadenectomy

13

Giovanni de Manzoni and Franco Roviello

## 13.1 Introduction

D2 lymphadenectomy is the standard of care for locally advanced gastric cancer according to most of the recent European guidelines [1–5]. The road that led to the establishment of this surgical standard has been troubled due to the negative results of all the European randomized trials that had compared the D2 lymphadenectomy with the more limited D1 dissection [6–8].

Low standardization of surgical procedures paradoxically both in the case of poor technical performance of involved surgeons, as in earlier studies, and of high surgical skills, as in the most recent trial, was responsible for the failure to demonstrate the oncological advantage of D2.

Indeed, both of the randomized clinical trials (RCT) performed in Europe in the 1990s, the UK Medical Research Council and Dutch Gastric Cancer trials [6, 7], failed to show any survival advantage of D2 dissection with respect to the D1 procedure. The main cause of such unexpected results was the inadequate preliminary experience of the participating surgeons in D2 lymphadenectomy. As such, the D2 arm was greatly disadvantaged by a more than doubled postoperative mortality, related to the high percentage of splenectomies and pancreatectomies, with respect to the D1 arm [7]. Of note, when considering only cancer-related mortality without postoperative mortality, a higher cancer-related survival was observed in the D2 arm than in the D1 arm of the Dutch trial after 15 years of follow-up [9].

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Moreover, poor compliance to D2 lymphadenectomy did not allow retrieval of an adequate number of lymph nodes [10], and it has been reported that major non-compliance, defined as the absence of retrieved lymph nodes in the nodal stations included in the intended extent of D2 dissection, occurred in 26% of the D2 procedures. Furthermore, a significant survival benefit was reported for the D2 compliant and contaminated procedures, namely in cases in which lymph nodes were yielded from all the stations of the intended D2 dissection and also from one or more stations outside the planned lymphadenectomy [10]. As regards the British RCT, the median number of retrieved nodes did not substantially increase from D1 ($n = 13$) to D2 ($n = 17$) lymphadenectomy [6].

More recently, another European RCT comparing D1 and D2 [8], although performed by experienced surgeons, avoiding pancreas resections, with high surgical quality control and acceptable postoperative morbidity and mortality, still failed to demonstrate a benefit of D2. The high proportion of early gastric cancers in both arms and the high median number of lymph nodes in the D1 arm ($n = 25$), likely due to contaminated procedures, could be the reasons for the trial's negative results [8]. However, based on a subgroup analysis, the authors concluded that in advanced, node-positive patients, D2 dissection is associated with a better survival [8].

Despite the evidence-based indications [11], D2 lymphadenectomy has been routinely performed in the last three decades in high-volume Western centers. The pancreas-preserving D2 procedure was reported to be safe, when performed in dedicated centers, and to be associated with improved oncological outcomes. On these bases, as well as due to the long-term results of the Dutch trial, D2 lymphadenectomy has currently reached its role as a standard in the surgical treatment of gastric cancer with curative intent in Europe.

## 13.2 Definition of D2 Lymphadenectomy

D2 lymphadenectomy is defined by the Japanese guidelines according to the extent of gastric resection. In detail, in the third and fourth edition of the Japanese guidelines [12, 13], D2 for subtotal gastrectomy is defined as the removal of stations 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 12a, while D2 for total gastrectomy includes stations 1–7, 8a, 9, 11p, 11d, 10, 12a.

Of note, in the recently published fifth version of Japanese treatment guidelines [14], station 10 has been excluded from D2 dissection for total gastrectomy, with tumors located at the upper third along the greater curvature being an exception to this rule.

The exclusion of nodes at the splenic hilum from the standard D2 total gastrectomy is based on the results of a recent randomized controlled trial [15] that enrolled 505 cases (excluding proximal tumors located along the greater curvature). More in detail, 254 patients treated with total gastrectomy plus splenectomy with complete removal of nodes at the splenic hilum were compared with 251 patients who

underwent total gastrectomy with spleen preservation, showing that splenectomy increases operative morbidity without improving survival and leading the authors to conclude that it should be avoided in total gastrectomy for proximal gastric cancer not invading the greater curvature. The splenic hilum should be dissected in cases of proximal tumors located along the greater curvature, as tumors at this site were the most frequent among those with positive lymph nodes at station number 10; the role of prophylactic splenectomy in such cases in order to completely remove the lymph nodes is still an unanswered question.

## 13.3 Beyond D2: D2+ and the Issue of Para-Aortic Nodal Dissection

The indication to dissect additional nodal stations beyond the standard D2 is considered by Japanese surgeons only in specific cases [13, 14]:

- Dissection of station 14v (superior mesenteric venous lymph nodes) for cancer of the distal stomach with metastasis to the station 6 lymph nodes (D2+ station 14v);
- Dissection of station 13 (posterior pancreas head lymph nodes) for cancer invading the duodenum (D2+ station 13).
- Dissection of station 16 (abdominal aortic lymph nodes) after neoadjuvant chemotherapy for cancer with extensive lymph node involvement (D2+ station 16).

Para-aortic nodes (16a2 and 16b1) together with other "posterior" stations (8p, 12p and 13) were historically included in the D3 dissection [16]. However, starting from the third edition of the Japanese treatment guidelines, routine dissection of lymph node stations beyond the standard D2 was no longer indicated. This was mainly based on the results of the JCOG 9501 trial [17] that investigated the role of "prophylactic" D2+ para-aortic lymph node dissection (PAND) compared to D2 in locally advanced gastric tumors without clinically evident metastases in the para-aortic area. As prophylactic D2+ PAND did not lead to any survival advantage over D2 but, on the contrary, it was associated with a higher rate of complications (especially ileus and lymphorrhea), the removal of 16 a2 and 16b1 stations was no longer recommended. In the same guidelines [12], "curative" D2+ PAND, i.e., dissection of the para-aortic area in cases of clinically detected lymph nodes at this site, was discouraged due to the poor survival of these patients.

Studies from our group comparing D2 with D3 lymphadenectomy in a clinical setting on patients not previously treated with preoperative chemotherapy, including both prophylactic and curative super-extended dissections, showed that D3 offers a better locoregional control in advanced gastric cancer with diffuse histotype compared to D2 [18]. Moreover, the long-term prognosis was better after D3 among T3 patients and T4a patients [19].

Of note, the indication for D2+ PAND was changed by Japanese surgeons in the era of multimodal treatment of gastric cancer. Indeed, nowadays, dissection of para-aortic area is allowed after neoadjuvant chemotherapy for cancer with bulky nodes in the D2 stations with or without lymphadenopathy in the para-aortic 16 a2–b1 area. Such change was due to the publication of a phase II trial [20] showing that in patients with clinically detected extensive nodal metastases (bulky nodes in the D2 stations) with or without lymphadenopathy in the para-aortic (16 a2–b1) region, a multidisciplinary treatment including two courses of neoadjuvant chemotherapy with S-1+ cisplatin followed by D2+ PAND leads to a 5-year survival rate of 53%.

In particular, in patients with clinically bulky nodes in the second-level perigastric stations, without preoperative evidence of PAN metastases, 5-year overall survival was 68% after "prophylactic" D2+ PAND; of note, para-aortic metastases were found in 5 of 24 patients in this setting. In patients with clinically detected PAN metastases without bulky N2 nodes, the 5-year overall survival was 57% after "curative" D2+ PAND; unfortunately, in patients with both initial bulky N2 and PAN metastases the 5-year overall survival was 17%. It should be remembered that in that phase II trial, peritoneal metastasis and positive cytology were excluded by staging laparoscopy before enrolment.

Although Japanese authors changed their view on PAND in patients with extensive nodal involvement in the context of multimodal treatment, the issue of the other "posterior" stations such as 8p and 12p has not been considered. These stations are not included in the standard D2 dissection by the third version of Japanese guidelines [12], while in the previous second version they were required in D3 dissection [16]. Indeed, all the posterior stations were excluded from the standard dissections since the publication of the JGOG9501 trial investigating the role of D2+ PAND compared to D2 alone in locally advanced gastric cancer, even though in that trial stations 8p and 12p were removed in both arms [21]. A recent observational study from our group [22] explored the benefit of "posterior" station removal in a large Western cohort undergoing D2+ dissection. A small proportion of patients (6.3%) had metastases in at least one of these posterior areas and radical surgery offered these patients a chance of a 5-year survival of 17%.

In view of the above considerations, in agreement with the Japanese authors, the current indication is to remove para-aortic nodes in a "curative" setting, i.e., in patients who have clinical evidence of para-aortic nodes before preoperative chemotherapy and then show clinical response at restaging examinations. However, with regard to the "prophylactic" setting, we believe that the indications could be wider that those considered by the Japanese authors, and that the benefit of removing the other posterior stations should be further evaluated. In an attempt to answer these questions we started a RCT to explore the role of "prophylactic" D2+ (including the para-aortic and other posterior stations) compared to the standard D2 in locally advanced gastric cancer patients treated with perioperative chemotherapy in the West (ClinicalTrials.gov NCT03961373).

## 13.4 Compliance with D2 Lymphadenectomy: The Delicate Balance Between Standardization and Tailoring of Lymphadenectomy

The compliance rates with D2 dissection of European surgeons in real life are largely unknown.

Many European countries have started recording data about the quality of surgery for gastric cancer at a national level, showing a significant improvement and higher rates of compliance with the guidelines after some years of auditing [23, 24].

In a recent study by our group [25], aiming at evaluating the compliance with D2 lymphadenectomy as described by the Japanese treatment guidelines, we showed that European dedicated surgeons perform an adequate lymphadenectomy (>15 nodes) in nearly all treated patients. However, there is still a high variability in the approach to D2, with the major determinants being tumor histology and the patient's general condition.

A great effort should clearly be made to definitively implement the standardization of D2 dissection in Europe. However, the above evidence raises the question of whether a certain level of variability would reflect more likely the efforts by expert surgeons to choose the best treatment for their individual patients rather than technical issues.

It would however seem from these results that more tailored treatment recommendations based on tumor and patient characteristics should be discussed in future projects for European guidelines.

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# Beyond Lymph Nodes: Splenectomy, Bursectomy and Omentectomy

14

Guido A. M. Tiberio, Luigi Marano, and Roberta Gelmini

## 14.1 Introduction

The primary and mandatory purpose of radical gastrectomy is to remove the entire neoplastic bulk. A sound surgical strategy and a correctly performed procedure have an impact on the locoregional control of the disease and influence both long-term survival and quality of life in a positive manner.

The entire surgical literature and clinical practice of the past 30 years struggled—and still does—in its search for the difficult balance of two apparently antithetic elements: the need to achieve optimal locoregional control of the disease and the biologic cost of surgical aggressiveness. In order to underline the critical value of this balance, it is important to remember that in the Western world the spread of standard D2 nodal dissection had been, and still is, heavily hampered by the results of the Dutch D1D2 and MRC trials. These were negatively affected, among other factors, by the high morbidity and mortality rates consequent to the inappropriate extension of the surgical demolition to the spleen and pancreatic tail, in order to facilitate removal of lymph nodes in stations 10 and 11. The advent of laparoscopic surgery further enlivened the debate—on the one hand, introducing undue shortcuts,

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aimed to adapt the oncologic standard to the new technical requirements, and, on the other, highlighting the advantages of the minimally invasive approach.

In this chapter we will discuss the role of splenectomy, bursectomy and omentectomy in the light of the recent literature, taking as a starting point the indications reported by the 2015 guidelines for gastric cancer staging and treatment of the Italian Research Group for Gastric Cancer (GIRCG) [1].

## 14.2 Splenectomy

In cases of advanced gastric cancer with direct infiltration of the spleen or pancreas, splenectomy or splenopancreatectomy are formally indicated in order to achieve a curative R0 resection. Besides this unequivocal indication, and despite the fact that 8–28% of proximal third gastric cancers metastasize to the splenic hilum nodes (station 10), the role of splenectomy as a facilitator of station 10 clearance is controversial and a certain trend toward a less invasive approach have been noted in recent years.

### 14.2.1 The Guidelines

In 2015 the Italian guidelines of the GIRCG [1] stated: "Splenectomy is generally associated with an increased risk of postoperative complications in GC surgery. Total gastrectomy with splenectomy should be recommended for tumors that are located along the greater curvature or when a macroscopic involvement of stations 4sa or 10 is present."

Along the same lines, the Japanese Gastric Cancer Treatment Guidelines 2018 (fifth edition) [2] modified the previous indication for standard D2 gastrectomy for advanced proximal gastric cancer. Historically, these included splenectomy for complete clearance of lymph nodes at the splenic hilum. At present the indications are as follows: "Spleen should be preserved in total gastrectomy for advanced gastric cancer of the upper stomach provided the tumor does not involve the greater curvature". Non-standard gastrectomy (lymphectomy beyond D2) "could be considered for dissection of station No. 10 with or without splenectomy for cancer of the upper stomach invading the great curvature", on condition that it can be conducted safely and although hard evidence is lacking.

### 14.2.2 The Literature

The cornerstone that sustains spleen-preserving procedures for proximal advanced gastric cancer not invading the greater curvature is the randomized, controlled, phase III trial conducted by the Japan Clinical Oncology Group (JCOG0110), whose results were already available in 2015 [3]. This trial indicated a low metastatic rate in station 10 nodes (2.4%), increased operative blood loss ($p = 0.025$) and

higher postoperative morbidity ($p = 0.0004$), mainly sustained by pancreatic fistula, in the splenectomy group and, most important, the non-inferiority of spleen-preserving surgery in terms of survival.

We do not have data from prospective trials focused on the subgroup of patients with cancer invading the greater curvature. However, a retrospective study from the National Cancer Center Hospital in Tokyo [4] reports a metastatic rate >15% in station 10 and suggests that splenic hilar nodes should be prioritized as a component of D2 dissection in this subgroup of patients. Interestingly, however, the authors did not record a survival difference according to the metastatic or non-metastatic status of station 10.

Okhura et al. focused on the specific population with proximal gastric cancer involving the great curvature of the stomach, revealing that splenectomy was associated with increased risk of morbidity without prognostic advantages, except for the specific subpopulation with Bormann type 1 and 2 tumors [5]. They reached similar survival results with patterns of recurrence characterized by a high proportion of peritoneal dissemination both in splenectomy and spleen preservation groups. However, the subset analysis stratified by the macroscopic type showed a marginally better survival in patients with Bormann type 1 or 2, suggesting that the aggressiveness of more advanced gastric cancer sustains such a high rate of peritoneal recurrence to jeopardize the effect of splenectomy. In different terms, metastasis in station 10 nodes confers such a poor prognosis to require an accurate balance between a survival benefit which seems small and the splenectomy-related biologic cost which is elevated.

The relevance and, possibly, the advantage of station 10 removal may be different in the light of a higher metastatic involvement rate. In fact, the Chinese paper by Liu et al. [6] reports a metastatic rate of 16.4% for station 10, and a significant survival benefit correlated to its clearance that should be performed with spleen preservation, both in open and laparoscopic procedures [7].

## 14.3 Bursectomy

The surgeon-bursectomy relationship had long been a difficult affair. Fascinated by the possibility to optimize surgical radicality and by the technical challenge, surgeons are at the same time threatened by its complications which may jeopardize the oncologic outcome. At present, bursectomy is rarely performed and, if so, it is reserved for selected patients candidate to non-standard multimodal management of their gastric cancer.

### 14.3.1 The Guidelines

In 2015 the Italian guidelines of the GIRCG stated: “When the posterior gastric wall serosa is infiltrated by the tumor (T4a), removal of the inner peritoneal surface of the bursa omentalis may be performed to remove microscopic tumor deposits in the lesser

sac. In T1–T2 tumors, bursectomy should be avoided to prevent injury to the pancreas and adjacent vessels". These recommendations were in line with those promoted by the Japanese Gastric Cancer Treatment Guidelines since the early 2000s [1].

However, in 2018 the fifth edition of the Japanese Gastric Cancer Treatment Guidelines [2] abandoned this position and considered that bursectomy should be no longer indicated on the basis that "… survival benefit of this procedure has been denied by a large-scale randomized trial (JCOG1001), not only for all patients but also for subsets with T4a tumors and tumors located in the posterior wall."

### 14.3.2 The Literature

Bursectomy prolongs duration of surgery and increases operative blood loss. These data emerge consistently from the analysis of the literature [8]. However, in the hands of high-volume surgeons, this procedure seems safe and may be easily included in standard gastrectomy, even if performed laparoscopically.

Monocentric studies were unable to demonstrate the impact of bursectomy on survival outcomes.

The Osaka Bursectomy Trial [9] was the first multicentric randomized controlled trial which explored long-term outcomes after prophylactic bursectomy in 210 patients with resectable gastric cancer. Surgery was the sole treatment strategy for gastric cancer in this cohort of patients. At a median follow-up of 80 months, the authors were unable to demonstrate the noninferiority of the omission of bursectomy. Subset analysis showed a trend toward better survival for middle or distal tumors invading the serosa.

These results were contradicted by the Japanese JCOG1001 study [10], a phase 3, open label controlled randomized trial enrolling 1204 patients for the final analysis. At the second interim analysis this study was interrupted by the Safety Monitoring Committee on the basis of futility: overall survival in the bursectomy group was lower than in the non-bursectomy group, with superimposable 5-year overall survival. Adjuvant S-1 based chemotherapy, routinely employed in stage II–III cases, was considered the main factor responsible for this result, suggesting that oncologic benefits associated with more invasive surgery, if any exist, could be more safely equaled by the anti-neoplastic efficacy of adjuvant chemotherapy. Alongside adjuvant chemotherapy, these results may be explained by the negative oncologic impact of major specific complications such as pancreatic fistula, observed in higher percentages than in the Osaka trial. Based on their data, the authors stated that bursectomy is not recommended at completion of standard surgery for resectable cT3 or cT4a gastric cancer.

### 14.3.3 May Bursectomy Still Have a Role?

The surgical indication for stage IV gastric cancer is in rapid evolution. In selected cases, surgery may play a significant role in the management of metastatic patients,

especially in the context of a multimodal management integrating surgery and chemotherapy, such as the setting of conversion therapy or HIPEC [11]. Although sound data do not yet exist and reported experiences only arise from tertiary institutions, bursectomy may still have a role in the management of those cases in which limited peritoneal involvement (PCI ≤6) is deemed surgically emendable and peritoneal metastases are detected in the lesser sac.

## 14.4 Omentectomy

The omentum plays an important role against abdominal inflammations and infections but, at the same time, it is the principal site of peritoneal surface metastasis in gastric cancer. Total omentectomy has been considered important to ensure elimination of micrometastases; however, there is no consensus regarding its real benefit. In fact, omentectomy increases the rate of splenic, colonic and mesocolic injuries and it is also associated with longer duration of surgery, especially when the laparoscopic approach is chosen.

### 14.4.1 The Guidelines

Omentectomy is not mentioned in the ESMO (European Society for Medical Oncology) or in the NCCN (National Comprehensive Cancer Network) guidelines.

The cited Italian guidelines of the GIRCG stated [1]: "The role of omentectomy is still questionable, particularly for serosa-negative advanced gastric cancer. Removal of the greater omentum is usually integrated in the standard gastrectomy for T3 or deeper tumors. For T1–T2 tumors, the omentum more than 3 cm away from the gastroepiploic arcade may be preserved."

The Italian recommendations were revitalized in the same terms by the Japanese guidelines in 2018 [2].

### 14.4.2 The Literature

The debate in the literature is mainly focused on the selection of patients that could take advantage from omentectomy.

The OMEGA Trial [12] prospectively evaluated 100 patients with gastric cancer undergoing gastrectomy with complete en-bloc omentectomy and modified D2 lymphadenectomy. Omental metastases were detected in five patients, two with linitis plastica and three with proximal tumor larger than 5 cm; all these five cases received R1 gastrectomy due to microscopic infiltration at either the proximal or distal margin. Considering that the incidence of metastatic involvement of the greater omentum is low and, when present, it is associated with surgically non-emendable features, the authors concluded that omentectomy as part of radical gastrectomy can be omitted.

Another Dutch group [13] reached opposite conclusions through a prospective analysis of a cohort of 50 patients. Omental lymph node metastases and omental tumor deposits were detected in 2% and 8% of cases, respectively. The authors advised omentecomy in all patients undergoing gastrectomy, since no predictive clinical variable was associated with omental involvement. However, also in this latter experience neoplastic involvement of the omentum displayed a negative prognostic value.

In a Japanese propensity score-matched retrospective cohort study [14] involving 526 patients after case-matching, the comparison between preservation and resection of the omentum during gastrectomy for advanced cancer (cT3–cT4a) did not show any difference in the rate or pattern of recurrence, nor different overall or relapse-free survival. Postoperative complications (intra-abdominal blood loss, intra-abdominal abscesses) were higher in patients undergoing omentectomy, while small bowel adhesions were lower in patients with omentum preservation.

The technical difficulties raised by omentectomy during laparoscopic procedures induced some authors to propose partial omentectomy as a possible alternative to total omentectomy for advanced cT2–cT3 gastric cancer. This procedure starts with the division of the great omentum 4 or 5 cm from the gastroepiploic arcade toward the origin of the left gastroepiploic vessels, whose omental branch must be preserved to prevent omental infarction. In their retrospective analysis, Kim et al. [15] demonstrated the advantage of omental preservations in terms of duration of surgery and postoperative complications, with a trend toward better oncologic outcomes in the partial omentectomy group.

At present, we are unaware of randomized controlled trials capable of offering a scientifically sound contribution to the debate. The results of the recently started JCOG1711, ROAD-GC trial will probably clarify the role of omentectomy in cT3 and cT4a gastric cancer [16].

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# Locally Advanced Gastric Cancer: The Edge of the Minimally Invasive Approach

15

Giovanni de Manzoni, Daniele Marrelli, Paolo Morgagni, and Franco Roviello

## 15.1 Introduction

Since the introduction of the laparoscopic technique as a treatment option for gastrointestinal (GI) cancer, safety in managing advanced cases has been one the main topics of debate. In 2008 a Cochrane review of randomized controlled trials (RCTs) on short- and long-term outcomes of laparoscopic surgery for colorectal cancer reported equal efficacy in terms of oncological results when compared with the open approach [1]. This evidence represented the basis for a massive use of the minimally invasive technique in GI oncology. However, a direct parallelism between colon cancer and other GI neoplasms is improper. More specifically, the differences between advanced colon and gastric cancer are, on one hand, the more demanding technical challenges of managing gastric cancer and, on the other hand, the different biology with a higher affinity for lymph nodes and peritoneum in stomach with respect to colon cancer. Specific data on the laparoscopic approach for locally advanced gastric cancer are not solid: most of the studies are designed to prove the non-inferiority rather than the superiority of laparoscopy over open surgery; very few patients treated with neoadjuvant therapy are considered; short follow-up periods are generally reported.

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Thus, the issue is not whether mini-invasive treatment for locally advanced gastric cancer is feasible, but what are its limits and long-term oncological results.

## 15.2 Evidence from the East

While the laparoscopic approach for early gastric cancer is widely accepted mainly based on two RCTs from the East [2, 3], until two years ago the evidence for routine use of laparoscopic gastrectomy to treat locally advanced cases was based on few available reports from Japanese and Korean high-volume centers (performing at least 100 open and laparoscopic gastrectomies per year) (Table 15.1). However, in the last two years, two of the most relevant RCTs (KLASS-02 and CLASS-01) comparing open and laparoscopic subtotal gastrectomy in advanced gastric cancer have provided relevant data [4–7]; the R0 resection rate was high with both the approaches, with a reduction of the complication rate in the laparoscopic group. The most important result was that no difference between laparoscopic and open surgery was reported in terms of 3-year overall survival (90.6% vs. 90.3%; respectively for KLASS-02 and 83.1% vs. 85.2%; respectively for CLASS-01); the same was shown for 3-year disease-free survival (80.3% vs. 81.3% for KLASS-02, and 76.5% vs. 77.8%; for CLASS-01). Nevertheless, some considerations are necessary: first, in both the studies a selection of patients based on lymph node involvement was made. Specifically, in the KLASS-02, only patients with lymph node metastasis in the field of D1 at clinical staging were enrolled and, in both trials, patients with bulky nodes were excluded. As a result, there was a high rate of early-stage gastric cancers improperly enrolled in both these trials.

With regards to lymph node retrieval, no differences were shown between laparoscopic and open surgery in both studies. Interestingly, by analyzing an RCT [10] specifically designed to evaluate the real compliance with D2 lymphadenectomy in laparoscopic and open sub-total gastrectomy, no differences in non-compliance rate with D2 (defined as the proportion of patients with more than 1 empty lymph node station of the planned dissection) between the two approaches was reported in overall series (mean number of lymph nodes: 39.7 for open vs. 37.0 for laparoscopy; $p = 0.168$). But, going deeper, more than 40% of cases were stage I at pathological examination, and the most surprising data was the higher rate of non-compliance with D2 dissection of laparoscopic gastrectomy in clinical stage III cancers: 52.0% of cases had a non-compliant lymphadenectomy by laparoscopic approach compared to 25.0% in the open group ($p = 0.043$); of note, this discrepancy could be even higher when considering the pathological stage.

For total gastrectomy, strong evidence is still not available even for the treatment of the early stages; in an advanced setting, a multicenter RCT comparing long-term results between laparoscopic and open total gastrectomy with D2 lymph node dissection is currently ongoing on behalf of the Korean KLASS group (KLASS-06) [14]. This trial will provide relevant results on this topic. Meanwhile, we have data from a recent meta-analysis on non-RCTs [15] published in 2020 that showed favorable postoperative results for laparoscopic gastrectomy with similar 5-year survival

**Table 15.1** Laparoscopic gastrectomy for locally advanced gastric cancer, summary of available randomized controlled trials

| | KLASS-02-RCT [4, 5] | CLASS-01 [6, 7] | Wang et al. [8] | JLSSG0901 [9] | COACT 1001 [10] | Cui et al. [11] | Shi et al. [12, 13] |
|---|---|---|---|---|---|---|---|
| Year | 2019, 2020 | 2016, 2019 | 2018 | 2015 | 2018 | 2015 | 2017, 2019 |
| Type | Phase III RCT | Phase III RCT | RCT | Phase II RCT | Phase II RCT | Single-center RCT | Single-center RCT |
| Surgical procedure | Distal gastrectomy | Distal gastrectomy | Distal gastrectomy | Distal gastrectomy | Distal gastrectomy | All | All |
| Oncological inclusion criteria (AJCC 8th ed.) | cT2-4aN0-1 (for site: #1–7) M0 | cT2-4aN0-3M0 | cT2-4aN0-3 M0 | cT2-4aN0-2M0 | cT2-4aN0-3M0 | M0 | cT2-4aN0-3M0 |
| Substantial exclusion criteria | N2-3 (for site: #8a–12a) Complicated cancer Neoadjuvant therapy | Bulky nodes Neoadjuvant therapy | Bulky nodes Complicated cancer Neoadjuvant therapy | N3 Bulky nodes Neoadjuvant therapy BMI <30 Kg/m$^2$ | Neoadjuvant therapy | Perforated cancer Conversion to open | Neoadjuvant therapy |
| Primary outcome | 3-year DFS | 3-year DFS | Morbidity-mortality | Anastomotic or pancreatic leak | D2 non-compliance rate | 30-day mortality | 5 year OS |
| Patients per arm | 525 pts | 528 pts | 220 pts | 90 pts | 102 pts | 148 pts | 164 pts |
| Oncological results | Open vs. Laparoscopic (*P* value) | Open vs. Laparoscopic (*P* value) | Open vs. Laparoscopic (*P* value) | Open vs. Laparoscopic (*P* value) | Open vs. Laparoscopic (*P* value) | Open vs. Laparoscopic (*P* value) | Open vs. Lap (*P* value) |
| *R0* | 98.6% vs. 98.1% ($p = 0.374$) | NR | NR | 100% | 95.8% vs. 100% ($p = 0.056$) | 95.9% vs. 86.5% ($p = 0.195$) | NR |
| *Mean no. of lymph nodes* | 47.4 vs. 46.6 ($p = 0.451$) | 36.9 vs. 36.1 ($p = 0.738$) | 31.4 vs. 29.5 ($p = 0.083$) | 47 | 39.7 vs. 37.0 ($p = 0.168$) | 30.1 vs. 29.3 ($p = 0.574$) | 32.2 vs. 31.6 ($p = 0.377$) |
| Short-term results | Open vs. Laparoscopic % (*P* value) | Open vs. Laparoscopic % (*P* value) | Open vs. Laparoscopic % (*P* value) | Open vs. Laparoscopic % (*P* value) | Open vs. Laparoscopic % (*P* value) | Open vs. Laparoscopic % (*P* value) | Open vs. Laparoscopic % (*P* value) |
| *Conversion to open* | 3.7% | 6.4% | 6.3% | 1.2% | 6% | 7.4% | 3.7% |
| *Anastomotic leak* | 1.1 vs. 2.0 ($p = 0.420$) | 0.6 vs. 1.9 ($p = 0.056$) | 1.8 vs. 1.4 ($p = 0.723$) | 1.2% | NR | 2.8 vs. 2.3 ($p$ = NS) | 0.63 vs. 1.23 ($p = 1.000$) |

(continued)

**Table 15.1** (continued)

| | KLASS-02-RCT [4, 5] | CLASS-01 [6, 7] | Wang et al. [8] | JLSSG0901 [9] | COACT 1001 [10] | Cui et al. [11] | Shi et al. [12, 13] |
|---|---|---|---|---|---|---|---|
| *Pancreatitis or pancreatic leak* | 0.7 vs. 1.7 ($p = 0.224$) | 0 vs. 0.4 ($p = 0.294$) | 0.5 vs. 0 ($p = 0.498$) | 3.5% | NR | NR | 0 vs. 0 ($p$ = NS) |
| *Duodenal leak* | NR | NR | NR | NR | NR | NR | 1.88 vs. 2.47 ($p = 0.685$) |
| *C-D ≥ IIIa* | 10.5 vs. 9.3 ($p$ = NS) | 2.7 vs. 3.5 ($p$ = NS) | 2.3 vs. 4.1 ($p$ = NS) | 5.8% | NR | NR | 1.26 vs. 1.86 ($p$ = NS) |
| *30-day mortality* | 0.4 vs. 0.4 ($p = 1.000$') | 0.4 vs. 0.4 ($p = 0.249$) | 0 vs. 0 ($p$ = NS) | 0 | 0 vs. 0 ($p$ = NS) | 0 vs. 0 ($p$ = NS) | 0 vs. 0 ($p$ = NS) |
| Long-term results | 3 years Open vs. Laparoscopic ($P$ value) | 3 years Open vs. Laparoscopic ($P$ value) | Open vs. Laparoscopic ($P$ value) | Open vs. Laparoscopic ($P$ value) | 3 years Open vs. Laparoscopic ($P$ value) | Open vs. Laparoscopic ($P$ value) | 5 years Open vs. Laparoscopic ($P$ value) |
| *OS* | 90.3% vs. 90.6% ($p = 0.961$) | 85.2% vs. 83.1% ($p = 0.28$) | NR | NR | NR | NR | 50.7% vs. 49.8% ($p = 0.767$) |
| *DFS* | 81.3% vs. 80.3% ($p = 0.726$) | 77.8% vs. 76.5% ($p$ = NS) | NR | NR | 81.9% vs. 80.1% ($p = 0.448$) | NR | 49.6% vs. 47.2% ($p = 0.654$) |
| Primary outcome results | No differences in 3-year DFS | No differences in 3-year DFS | No differences in morbidity-mortality | Anastomotic or pancreatic leak comparable to literature | No differences in D2 non-compliance rate | No differences in 30 day mortality | No differences in 5 year OS |
| Main limits | Reduction in morbidity is mainly related to C-D grade II 33–35% of stage I | 12–16% of stage I Near 50% of N0 Mean BMI 22.7 | 31–34% of stage I Near 45% of N0 Mean BMI 23.5 | Non-comparative data 46.7% of stage I | D2 non-comp. different in stage III 37–42% of stage I Mean BMI near 23.5 | DG and TG considered together Mean BMI near 23.5 If conversion, excluded from analysis | 6–10% of stage I DG and TG considered together Mean BMI near 20.5 |

*RCT* randomized controlled trial, *DFS* disease-free survival, *OS* overall survival, *BMI* body mass index, *NR* not reported, *NS* not significant

rate when compared to open total gastrectomy. However, still the number of dissected lymph nodes was higher in the open approach, and the good survival results could be affected by the large number of stage II cancers in the entire series.

In summary, the Asian literature gives substantial contribution to the topic of laparoscopic gastrectomy for advanced gastric cancer showing promising even though not exhaustive results; nevertheless, in the West the epidemiology of stomach cancer, the characteristics of patients, and the therapeutic strategies are so different from those in the Far East that the experiences are not directly applicable, as discussed in detail in the following paragraph.

## 15.3 Evidence from the West

In Western countries, the "stereotype" of the patient with gastric cancer is an old, obese subject most likely suffering from proximal advanced cancer with bulky nodes; another relevant aspect is the high rate of European patients that undergo surgery after neoadjuvant treatments. In this context, it is questionable whether to apply the recommendations coming from Eastern trials that excluded patients treated with neoadjuvant therapy, cases with bulky nodes as well as those with extensive lymph node involvement.

With the publication of a European multicenter RCT (STOMACH trial) [16] some of these concerns were apparently overcome, given that in a post-neoadjuvant setting laparoscopic total gastrectomy provided similar results in terms of retrieved nodes compared to the open approach. A substantial result of this study is the comparable compliance between the two techniques in different D2 nodal stations. Similar outcomes were shown in postoperative complications and 1-year survival rates. Late follow-up will provide the most crucial data; however, sample size was calculated for lymph node dissection, not for long-term survival; moreover, this trial is underpowered because of slow accrual, even if T4 cancers, originally excluded in the study design, were later considered. Despite these considerations, the STOMACH trial is a "mirror of the European reality" and a good starting point for further studies.

Other studies show good results in terms of quality of life, but a high incidence of esophagojejunal leakage after laparoscopic total gastrectomy.

To summarize, several questions still remain unanswered. First, the real compliance of lymph node dissection in cases with bulky nodes, in obese patients or in advanced stages after neoadjuvant therapy. Moreover, there is weak evidence in long-term results, mainly in serosa-arising cancers with poorly cohesive histology that have the highest incidence of peritoneal relapse. Given the different characteristics in tumor spread, response to therapy and recurrence pattern, an accurate analysis according to the different histological and molecular subtypes should be considered in future studies.

## 15.4 The Edge of Evidence or the Edge of Technique?

Discussion on the appropriate treatment of locally advanced gastric cancer is not over. Several hot topics are addressed throughout the present book: most of the debate is about the pertinence of a technique in local control of cancer. The attempt is to define the perfect balance between the risks and benefits of procedures; what is taken for granted is that the procedure is feasible and reproducible, an assumption that is certainly true in open surgery, but that needs to be proven in minimally invasive surgery.

After the publication of the JCOG1001 trial [17], bursectomy is no longer indicated even in T4a cancers. Nevertheless, patients not treated with adjuvant chemotherapy seemed to have a survival benefit from a more aggressive surgery.

In 2017 Sano el al. published an RCT denying the positive role of splenectomy in survival, but patients with macroscopic lymph node metastasis at the splenic hilum or with tumors involving the greater curvature were excluded [18].

The most important consideration, however, regards the role of para-aortic lymphadenectomy that is no longer routinely performed in the prophylactic setting, but in the era of multimodal treatment the role of D3 lymph node dissection with both curative and prophylactic intent seems to be relevant in some subgroups of patients.

This brief discussion just to underline that performing safely a total gastrectomy with D2 lymphadenectomy may not be enough to control the neoplastic potential of locally advanced gastric cancer.

Technical aspects of procedures that go beyond the standard laparoscopic gastrectomy with D2 lymphadenectomy have been well described by expert surgeons; however, the experiences provided by these authors cannot be transferred to clinical practice because the reproducibility of these complex procedures is demanding.

## 15.5 Final Considerations

***First*** When dealing with cancer surgery, technical aspects, although relevant, are secondary to the oncological aspects. Thus, assessing the appropriateness of the laparoscopic approach means considering the impact of the technique in the different histological and molecular subtypes: it is no longer acceptable to ignore the tumor biology.

***Second*** Not everything is clear about the extension of dissection that is able to control each case of locally advanced gastric cancer: during the introduction of a new technique, the indications should be limited to what is standard and well established; therefore, an accurate selection of the patient is needed. Surgeons should not be dominated by the technique, but they should rule the technique in order to offer the best treatment for each single patient.

***Third*** Obsessively waiting for clinical evidence way may be harnessing. No doubt, evidence needs to be provided, but meanwhile a step-by-step progression and an accurate evaluation of results is necessary to avoid suboptimal care. An example of this is cervical neoplasia, for which laparoscopic hysterectomy was stopped because of the lower rates of disease-free survival and overall survival compared to open surgery [19]. Therefore, defining the limits, such as surgical volume, morbidity, mortality and survival rates for each center is crucial.

***Fourth*** The Japanese guidelines state that there is currently no evidence to recommend a laparoscopic approach: such a cautious attitude should not be ignored.

*In short, the conclusion should not be reduced to "feasible".*

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# Impact of Hospital and Surgeon Volume on the Outcomes of Gastric Cancer Surgery

16

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## 16.1 Introduction

Gastric cancer (GC) affects every year over 1,000,000 people with 783,000 deaths [1]. Surgery, in the context of multimodal therapy, is the cornerstone of GC treatment. Standardized D2 lymphadenectomy, due to its superior outcomes in terms of locoregional recurrence and disease-specific survival, is currently regarded as the gold standard for surgical treatment with curative intent worldwide [2–6]. D2 lymphadenectomy has also been associated with higher postoperative morbidity and mortality [3] and therefore it is not universally accepted that this procedure could be performed in non-experienced centers [7]. This recommendation has been based on studies reporting better outcomes when patients receive gastrectomy in high-volume hospitals or by high-volume surgeons. In recent years, evidence from these studies led to initiatives towards centralization of GC treatment by many countries [8–10]. Controversies still exist, related to the unclear effect of hospital versus surgeon volume [11–15], and to the feasibility and possible disadvantages of centralization in many sociocultural and logistic settings [16–18]. In this chapter, we summarize the main topics of debate in this field and present the current available evidence.

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## 16.2 Hospital Volume: Underlying Implications

Since the first report of Luft et al. in 1979 [19], a growing number of studies confirmed a significant reduction in surgical mortality when surgical procedures are performed in high-volume hospitals [20, 21]. This has been consistently reported even for surgical oncology procedures [22–24]. Many authors underlined how this is probably dependent on increased surgical expertise and higher volume of cases for surgeons in high-volume centers. However, the status of high-volume hospital is regarded as a proxy not only for surgeons with a high-volume of procedures, but even for other measurable and non-measurable variables such as case-mix (complexity of operation, comorbidities), better facilities in terms of perioperative management (intensive care units, trained anesthesiologists and radiologists, trained nurses, availability of other specialists) or management of postoperative complications (24/7 assistance from experienced physicians, interventional radiology, etc.) and qualified and controlled processes of care as the appropriateness of indication obtained through multidisciplinary tumor boards. Most of these aspects could have an adjunctive direct influence on short-term outcomes such as postoperative morbidity and mortality, especially on the "failure to rescue" phenomenon (the incapacity to avoid the shift from minor to major complications and from complications to mortality) [11, 16, 25, 26]. Influence on long-term outcomes could also be due to other factors, including the appropriateness of patient selection for neoadjuvant and adjuvant therapy, the type of surgery, the technical skills of the surgeon, and the availability of a specialized pathologist to appropriately stage the disease (i.e., through a sufficient lymph node count) [16, 27]. Interpretation of studies on this topic requires caution, as the definition of volume may have significant variation among countries (or regions within countries) due to the different incidence of disease [28–30] and different baseline patient and tumor characteristics (i.e., tumor stage, older patients, patients with specific comorbidities) [31]. Therefore, studies and reviews adjusted for case-mix are usually preferable.

## 16.3 Learning Curves and Definition of "High-Volume" in Gastric Cancer Surgery

In the Western and Eastern scenario, there are considerable differences in the definition of "high volume".

In Eastern countries, due to the higher incidence of GC, surgeon training is intuitively advantaged, as impressive hospital- and surgeon-volumes have been reported for standard as well as for minimally invasive procedures [32, 33]. However, even in this setting, the length of the learning curve and the measures for hospital- and surgeon-volume have not yet been standardized. A 2016 multicenter Korean study examined the learning curves of nine surgeons, concluding that the optimization of

survival is obtained after at least 100 gastrectomies. However the study detected the lowest survival rate in patients treated by surgeons with an experience of 50–100 cases, possibly because of overconfidence with the surgical technique [15, 34]. A 2017 Korean study investigated the difference between two hospitals, one defined as high-volume (about 500 gastrectomies/year) and the other as low-volume (about 50 gastrectomies/year). In both hospitals, the surgeons were qualified in upper GI surgery and had at least a 7-year experience. Treatments were given according to standard guidelines. This study found only a slightly lower overall and disease-specific survival in the low-volume center, with no significant difference between the two centers. This result was interpreted as a sufficient surgeon learning curve and a valuable quality of care process in the low-volume hospital [35]. Of note, in this study, the "low-volume" center had higher volume than many of the "high-volume" Western centers.

In the Western setting, the lowest incidence of GC is paired by lower mean volumes reported by hospitals and surgeons. Reports on the required learning curve for gastrectomy are heterogeneous even in Western centers. A minimum number of 15–25 cases is considered the threshold to optimize the learning curve in terms of postoperative outcomes [36–38]. A Dutch study analyzed the learning curve for minimally invasive gastrectomy, reporting a reduction of the conversion rate and an increase in the lymph node yield after the tenth case [39]. The discordancy with the Eastern data and the limited number of patients with GC to which surgeons are exposed during training led to questioning the quality of gastrectomy in the West [40–42]. The recent introduction and the ongoing validation of the indications for minimally invasive gastrectomy (MIG) add even more complexity to this matter mainly for the even poorer learning opportunities for trainees [40] relate to the appropriate indication to MIG. An excessive implementation of centralization could further reduce the access to specialistic surgical training and limit the number of qualified (and up-to-date) GC surgeons across the country [43].

The definition of low- and high-volume hospitals varies significantly across Western countries, and the minimum threshold of cases/year to allow the performance of gastrectomy is not regulated in every country. A 2013 North American consensus study concluded that surgeons operating ≥11 GC cases per year could safely perform open gastrectomy or D2 lymphadenectomy, while ≥20 cases per year were required for multivisceral resection or MIG. Hospital volumes ≥21 cases per year was considered appropriate for any GC procedure [44]. In most European studies the definition of high-volume centers required a number of at least 20–40 gastrectomies per year [9, 11, 28, 45]. In Italy, a minimum number of 25 cases is the cut-off for representing a surgical oncology referral center for GC [46]. However, a 2017 Italian national report covering the years 2012–2015 identified 40 cases per hospital and/or per operational unit as the cutoff for a relevant decrease in mortality. According to this threshold, only 33 centers in Italy could be classified as high-volume. Nevertheless, only 10.7% of the total number of gastrectomies were performed in these centers [47].

## 16.4 Hospital and Surgeon Volume in Relation to Short- and Long-Term Outcomes After Gastrectomy

Many Western studies have focused on the actual effect of hospital volume on the short- and/or long-term outcomes after cancer surgery, to clarify the specific effect magnitude of hospital volume and therefore identify for which outcome a high volume would fully explicate its benefit.

In a 2008 study from Bilimoria et al., short- and long-term outcome benefits were quantified for different fields in surgical oncology using the US National Cancer Database. They analyzed the distribution of 27,420 GC patients operated on in 1405 hospitals, identifying lowest-volume hospitals as those performing <4 and highest-volume hospitals as those performing >17 gastric resections *per* year. The comparison between lowest- and highest-volume hospital documented an increased risk of perioperative death and a poorer 5-year survival for patients treated in lower-volume hospitals, and estimated 179 perioperative deaths and 493 long-term deaths could have been avoided in the highest-volume hospitals [16], data confirmed in another US study published in 2018 [13]. In data from the UK National Esophago-Gastric Cancer Audit for the years 2011–2013, the median (inter-quartile range) of the annual hospital and surgeon volumes were 110 patients (82–137) and 13 patients (8–19), respectively. The 30- and 90-day mortality rate was <5% and the anastomotic leakage rate was 6.3%. After adjustment, there was a lower 30-day mortality and a lower anastomotic leak rate in hospitals with higher volumes. Higher surgeon volume was associated with (and explained most of) the lower anastomotic leak rate. This study concluded that surgeon and hospital volume probably represent different aspects of quality of care. It did not analyze long-term outcomes [12]. In a retrospective review of data from the CRITICS trial, Dutch hospital volumes were ranked as very low (1–10), to low (11–20), medium (21–30), and high (31 or more) according to the volume of gastrectomies; the highest surgical quality was detected for high-volume hospitals, even though there was no significant difference in postoperative morbidity and mortality between categories [8]. A subsequent retrospective review of the CRITICS trial reclassified hospitals as low-volume (1–20 surgeries/year) and high-volume (≥21 surgeries/year) finding better overall and disease-free survival in high-volume hospitals [48].

Two systematic reviews of adjusted studies reported a reduction in mortality for high-volume hospitals, as well as a reduction in mortality for high-volume surgeons performing gastric surgery [49, 50]. One of the included studies presented the different combined effects of high- and low-volume hospitals (>54 cases/year and 1–54 cases/year, respectively) and high- and low-volume surgeons (>9 cases/year and 1–9 cases/year, respectively). In this study, the best outcomes in terms of postoperative mortality were obtained by high-volume surgeons in high-volume hospitals, followed by low-volume surgeons in high-volume hospitals, high-volume surgeons in low-volume hospitals and low-volume surgeons in low-volume hospitals [51]. A systematic review by Mukai et al., including 23 studies, confirmed the difference in postoperative mortality between high- and low-volume hospitals and surgeons. Less evidence was found for postoperative morbidity. One study reported

a better 5-year overall survival for patients operated on by specialized surgeons, while another reported a beneficial effect of surgeon age and volume on 6-month mortality. Instead, there were other studies that did not demonstrate an association between hospital volume and long-term survival, including a correlative analysis of the Japanese randomized trial JCO9501 [14].

Even though many factors may be involved, it seems probable that a surgeon's longer learning curve and a greater clinical experience are important factors in determining patient outcomes. Apart from the purely technical skills, it has been advocated that the profile of a gastric surgeon requires a broader understanding of GC biology and an active involvement in clinical, translational, and basic research [33]. All these skills are easier to develop in high-volume centers. Nevertheless, other authors have questioned that some factors different from the surgeon volume may also influence outcomes, and that there is the possibility that surgeons with low volume for gastrectomy but excellent outcomes and surgeons with high volume but poor outcomes exist [52]. Moreover, a high-volume surgeon settled in a low-volume hospital could guarantee standard outcomes as well. Due to the frequent low transparency of hospital data, these hypotheses remain speculative and the relative quality of the different centers very difficult to assess, leaving hospital volume as one of the simplest and most reliable indicators of quality [53].

## 16.5 Need for Centralization in the Western Setting: Balancing Advantages and Disadvantages

Recent years have seen a tendency towards centralization. Studies from countries that promoted strict centralization campaigns have reported an improvement in perioperative and even in oncologic outcomes (lymph node count) for patients treated in higher-volume centers [12, 54, 55], even though these results were not always univocal. In a 2016 study, Busweiler et al. analyzed the process of centralization of GC surgery and the associated clinical outcomes in the Netherlands. They introduced a surrogate variable for upper GI expertise, namely, the composite volume of upper GI cancer resections (including gastrectomies, pancreatectomies and esophagectomies for a total number of $\geq$40) noticing that centralization was extremely successful as 5.8% GC cancer patients were treated in high-volume centers in 2005 compared to 80% in 2014. They identified a significant advantage in terms of higher lymph node count, lower 30-day mortality and higher overall survival for patients treated in high-volume centers. However, significance was lost after case-mix adjustment. Only in the subgroup of elderly patients did they find a significant decrease in postoperative mortality for high-volume centers [11].

The trend towards centralization has to deal with real-life patient behavior and preference. Indeed, opposed to its clear benefits, centralization also has potential disadvantages in terms of patient comfort, due to the long travel times and possible social and familial isolation [16], of continuity of care, of logistic problems, and even of safety, in case of urgent need for readmission. Moreover, information on the volume and mortality rate *per* procedure of the different hospitals may not be widely

available to the public [17] and therefore not implicated in the patients' choice of whereabouts of treatment. One field of research is investigating the patient decision-making process. In one Dutch paper, elderly patients showed a tendency to be treated in a nearby hospital out of convenience [11]. In one US paper, patients with a worse comorbid status and a higher pathological stage showed a trend for being treated in low-volume hospitals. Patients treated in low-volume hospitals were usually of racial/ethnic minorities and had lower incomes [13]. In another US paper, travel distance seemed the most important factor influencing patients to seek treatment in lowest-volume centers near to their home [56]. In a recent US paper analyzing the travel patterns in the state of California, most of the patients undergoing gastrectomy for GC did so at hospitals nearest to their homes, or even traveled past highest-volume hospitals to reach lower-case ones in 27.9% of cases. Only 19.2% patients were treated in teaching hospitals. Travel patterns were related to ethnicity, type of insurance, and residency in urbanized vs. rural areas. The findings of this study suggested that most patients were prepared to travel long distances to receive specific care, but they were influenced by factors other than hospital outcomes or they may not know/consider them in their selection process [17].

Last, as addressed by some studies, the process of centralization should be correctly targeted on hospital and personnel capacity, as reaching a limit could create a paradoxical decrease of the quality of care even in high-volume centers [57].

For these reasons, safeguarding the possibility for lowest-volume centers to appropriately deal with GC patients according to patient trends and geographical needs remains very important. Standard quality upper GI surgical fellowships and training in higher-volume hospitals for the health personnel may be a solution [33]. Moreover, quality assurance programs and clinical audits have been proposed as another strategy to improve the clinical outcomes [44, 58]. Possible solutions to the fragmentation of the process of care consequent to an increase in centralization include the implementation of the current hospital and territorial clinical networks, in particular of referral pathways and oncology networks, which should be able to guarantee standard care from a multidisciplinary point of view [18].

In Italy, a centralization process has not yet been introduced for GC, nor for other malignancies. A referral pathway for cancer patients has been introduced only in 7 out of 21 Italian regions (namely Tuscany, Lombardy, Piedmont, Veneto, Aosta Valley and Liguria), with the vast majority organized according to a hub-and spoke model. Furthermore, the latest Italian National Health Care Outcomes Program – Piano Nazionale Esiti (PNE) tracked 5873 GC resections performed in 498 Italian hospitals in 2018, reporting a mean number of GC resections/hospital/year of $11.8 \pm 263.3$, ranging from 1 to 127. In 2018, 40.4% of the hospitals treating patients with GC performed less than 5 procedures/year. When categorizing institutions according to volume (1–3 vs. 4–7 vs. 8–16 vs. 17–127 resections/year), the mean mortality was of 7.7% in institutions performing 1–3 resections, compared to a mean mortality rate of 4.7% in the highest-volume institutions (unpublished data). It should be noted, however, that the number of GC resections in each Italian province does not mirror the actual number of GCs diagnosed in the same region. Indeed, the PNE registry highlighted that 50.5% of residents in Calabria who had a

diagnosis of GC requiring surgery were treated in another province. The pattern of Italian health-related travels (patients leaving their regions to receive gastrectomy) usually follows a south-to-north trend, being the highest in Calabria, followed by Basilicata (37.1%) and Molise (35.9%), with the lowest rates detected in Lombardy (2.0%), Friuli Venezia Giulia and Veneto (3.5%) [59].

## 16.6 Conclusions

In light of the current evidence, future Western research should be directed to quantify the benefit conferred by the hospital and surgeon volume on the outcomes after gastrectomy. Results should be evaluated to codify volume thresholds according to the possible benefit for patients treated in different centers. These elements should be related to the reality of the different countries, in terms of actual results by center and in terms of logistics. Issues associated with the geographical location of the different hospitals and with other sociocultural (country-specific) needs have to be accurately defined, in order to understand how to promote access to high-volume centers for patients that will have a perceivable benefit from being treated in a specific high-volume setting. At the same time, the possible defects in the process of care of the lowest-volume centers have to be clarified in order to be adequately managed and improved, to guarantee safety for those patients that have a high probability of being treated in low-volume settings. Surgical training has to be further standardized with dedicated fellowships or defining the minimal skills-volume load required to perform certain surgical procedures in the different settings. The benefits of minimally invasive treatment should be further investigated and linked with specific case-volume outcomes, and particular attention should be given to include minimally invasive surgery training in the educational pathway of upper GI specialists. For this purpose, networking among centers should be promoted (i.e., surgeons and other personnel could be trained, even on rotation, in high-volume centers). Information campaigns for patients have to be promoted as well. Hospital data should be transparent and easily available to increase patients' awareness and give them elements to help them decide where to be treated. On a national scale, infrastructure implementation and welfare solutions should be developed to support patients that could have perceivable benefits from being treated in high-volume centers, especially when these are located at a long travel distance.

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# Therapeutic Approach to cT4b Gastric Cancer

17

Daniele Marrelli, Fausto Rosa, Giulio Bagnacci, and Chiara Defraia

## 17.1 Introduction

Locally advanced gastric cancer refers to tumors infiltrating adjacent organs or structures without distant metastasis, and this unique condition is staged cT4b in clinical practice. Gastric and additional organ en-bloc resection may be the only way for cure. However, radical resection for cT4b gastric cancer may result in complex operations, and potential postoperative complications in some cases, especially when the pancreas and liver are involved [1–5]. Simultaneously, cT4b patients often present with distinct lymph node metastases and peritoneal spread due to the perforation of serosa, which contribute to poor survival. Therefore, the role of multivisceral resection for cT4b gastric cancer remains controversial [6–10].

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## 17.2 Epidemiology

In Western series, due to the lack of screening programs, a significant proportion of patients with gastric carcinoma are diagnosed in advanced stages; T4b tumors represented 8.5% of a series including 2416 patients in the Italian Research Group for Gastric Cancer (GIRCG) database [11], 9.4% of 16,722 cases in the US Surveillance, Epidemiology, and End Results (SEER) database, and only 3.6% of 78,648 cases in the Japanese Gastric Cancer Association (JGCA) Registry [12]. Furthermore, most cT4 cases are poorly differentiated/diffuse histotypes; this implies an expected increase in the rate of these advanced forms, in consideration of the recently reported epidemiological trends in Western countries [13].

## 17.3 Diagnosis

A preoperative diagnosis of adjacent organ infiltration may be difficult in several cases. At CT scan, obliteration of the fat plane between the gastric lesion and adjacent organs or their direct infiltration are considered criteria for cT4b [14] (Fig. 17.1). However, preoperative accuracy of diagnostic imaging ranges between 43% and 88% [15]. Magnetic resonance imaging (MRI) and positron emission tomography (PET) in general do not provide significant improvements for clinical staging. As such, in suspected cases a staging laparoscopy is advised. This is important for a correct diagnosis of a cT4b stage, to assess the possible involvement of the peritoneum, and to perform washing cytology, which is frequently associated with an advanced T stage.

## 17.4 Upfront Surgery

Several studies evaluated the clinical impact of the combined resection of involved adjacent organs. The most common combination of resected organs is the stomach and the spleen, pancreas, or transverse colon. Many studies have investigated the influence of the additionally resected organ, but the data are conflicting. In some studies [16, 17], patients with colon or mesocolon invasion had a significant survival advantage over those with other organ invasions.

Some authors showed that spleen involvement was a negative predictor for survival [3, 16, 17], while others took the opposite view [5, 18]. The data regarding pancreatic resections are similar and are often reported together with those for splenectomy [19–22]. However, beyond the reported differences, most recent series, including the GIRCG study, conclude that on multivariate analysis multivisceral resection is not an independent predictor of poor survival [2, 3, 5, 21].

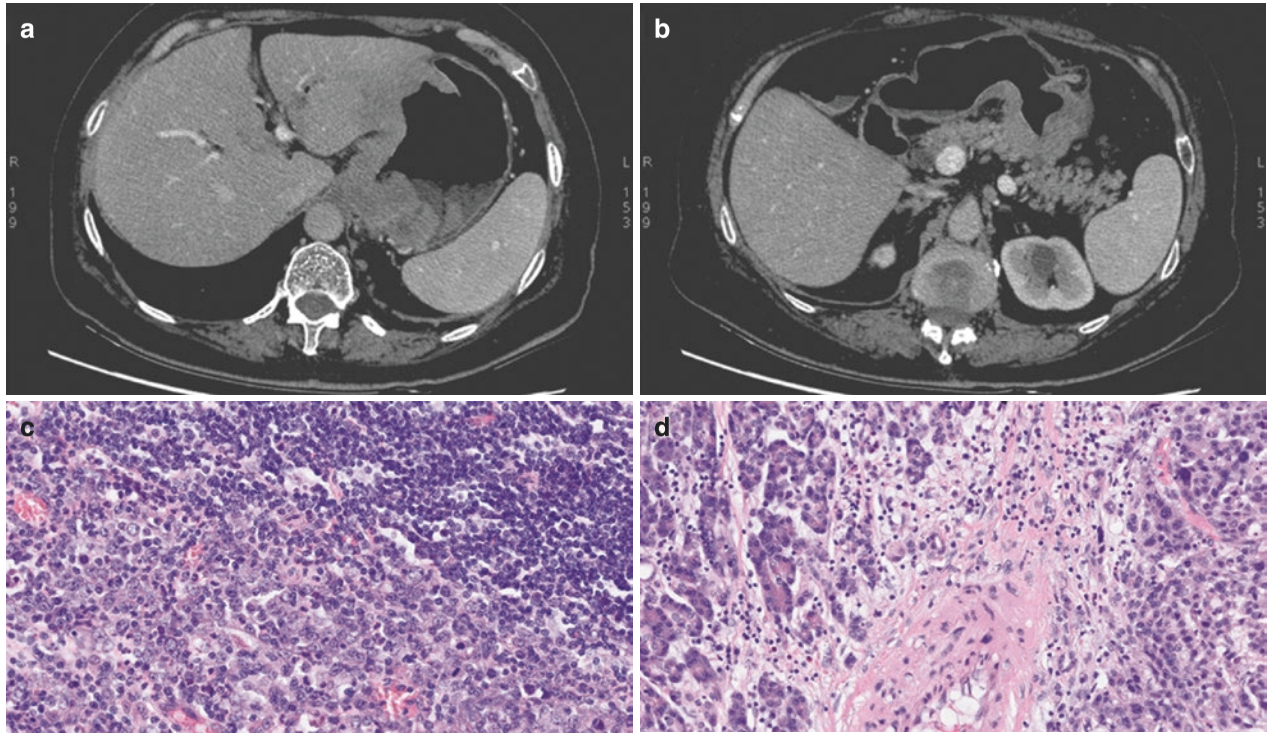


**Fig. 17.1** Computed tomography scan shows direct infiltration of the left liver lobe (**a**) and pancreas (**b**) by medullary-type gastric cancer. (**c**) Gastric carcinoma with lymphoid stroma: medium- and large-sized cells with round nuclei, scattered chromatin and one or more prominent nucleoli. Dense lymphoid infiltrate along the border of tumor invasion is visible at the top of the image. Notice the presence of atypical mitoses (HE; 40×). (**d**) Neoplastic infiltration of the pancreas: neoplastic cells (right), infiltrating pancreatic tissue (left); atypical mitoses and pleomorphic nuclei are easily recognized (HE; 40×). The stage of this tumor was: pT4bN2M0. Her-2: negative. High microsatellite instability

## 17.5 Postoperative Outcomes

Patients undergoing extended resections may experience postoperative complications and mortality. Morbidity rates in patients undergoing additional organ resection with gastrectomy are reported to be higher than in patients undergoing gastrectomy alone [22, 23]. The increase in overall complications, combined with low survival probability, could explain the general skepticism regarding these procedures in patients with T4 disease.

Some studies evaluating outcomes of patients undergoing total gastrectomy alone or with splenectomy, pancreaticosplenectomy, or esophagectomy showed a survival disadvantage for gastrectomy with additional organ resection [16, 20, 24, 25], above all when more than one organ is resected [1, 4, 8].

Recently, a large retrospective study by Aversa et al. [15] found that there was no association between gastrectomy plus multivisceral resection and short- or long-term mortality.

As shown in Table 17.1, taking into account the poor homogeneity of the studies in the literature, main published series have demonstrated that gastrectomy with additional organ resection for gastric cancer can be achieved with acceptable perioperative morbidity and mortality, and some authors [2] recommend performing resection in patients with T4b gastric carcinoma regardless of surgical curability (R status).

## 17.6 Long-Term Results and Prognostic Factors

The main bias of the retrospective studies that examined multivisceral resections is patient selection, since they often included advanced-stage disease, peritoneal carcinomatosis or metastatic spread. Furthermore, peritoneal washing cytology was rarely examined. These aspects could explain the large differences in long-term results among the different reports. However, most of them showed an advantage, in terms of 5-year survival, in patients who underwent gastrectomy with multivisceral resections when compared with gastrectomy alone or palliative procedures [1, 6, 15, 23, 26].

In selected cases, extended surgery could allow local control of the disease with non-negligible 5-year survival rates (15.4–38% in the different series) as shown in Table 17.1.

Prognostic factors for patients with T4b gastric cancer were also investigated but a great variability exists in the literature. Nonetheless the features most often identified as independent prognostic factors are: completeness of resection, number and type of resected organs, lymph node metastasis, and tumor dimension.

**Table 17.1** Published series and results on therapeutic approach to cT4b gastric cancer (2000–2020)

| Series | N. of cases | Postoperative morbidity | Postoperative mortality | 5-year survival[a] | Negative prognostic factors |
|---|---|---|---|---|---|
| Isozaki et al. 2000 [18] | 86 | NR | NR | 35% | Tumor location, N+, depth of invasion, extent of lymph node dissection |
| Saito et al. 2001 [10] | 156 | NR | NR | 38% | R+ resection, peritoneal and liver metastasis |
| Dhar et al. 2001 [16] | 150 | 31.3 | 2.6 | 25.1 | Splenectomy, esophageal invasion |
| Piso et al. 2004 [19] | 33[b] | 36 | 9 | 24 | R+ resection |
| Carboni et al. 2005 [6] | 65 | 27.7 | 12.3 | 21.8 | R+ resection |
| Martin et al. 2002 [1] | 268 | 33 | 3.7 | 32 | Depth of invasion; nodal status |
| Kim et al. 2006 [2] | 95 | NR | NR | 19.9 | N+ status |
| Oñate-Ocaña et al. 2008 [9] | 74 | 39 | 10.7 | 35 | M+ status, albumin levels, presence of ascites |
| Kim et al. 2009 [26] | 34 | 11.7 | 0 | 37.8 | R+ resection |
| Ozer et al. 2009 [8] | 56 | 37.5 | 12.5 | 28.1[c] | Advanced age, N+ status; resection >1 additional organ |
| Jeong et al. 2009 [5] | 47 | 31.7 | 3.3 | 31.5 | R+ resection, N3 status |
| Fukuda et al. 2011 [27] | 53 | 28.6 | 4.2 | 34.1 | Peritoneal cytology |
| Pacelli et al. 2013 [3] | 112 | 33.9 | 3.6 | 27.2 | R+ resection, N status |
| Mita et al. 2017 [21] | 103 | 37.9 | 1 | 47.7[c] | R+ resection |
| Tran et al. 2015 [22] | 159 | 59 | 5.2 | 20 | Pancreatic resection |
| Aversa et al. 2020 [15] | 347 | NR | 8.8 | 19 | R+, N+ |
| Yang et al. 2020 [23] | 153 | 13[d] | 1.3 | 15.4 | R+ resection, extensive lymph node involved (>15), vascular cancer emboli, postoperative chemotherapy |

*NR* not reported
[a]Survival rate of R0 resected patients
[b]Only pancreatic resections
[c]3-year survival
[d]Only major complications

## 17.7 Completeness of Resection

The main prognostic factor, confirmed in almost every study, is completeness of resection. The 5-year survival rate in patients with T4b gastric cancer undergoing curative resection (R0 resection) ranges from 23% to 46% (Table 17.1); this rate decreases to 17.5–0% in R+ resection [2–6, 23]. Although the study of Kim et al. [2] recommended resection in patients with locally advanced gastric carcinoma regardless of curability, the risk/benefit ratio of such procedures should be carefully evaluated.

## 17.8 Number of Resected Organs

According to some studies, the number of resected organs is associated with a poor prognosis [1, 4, 8, 21, 22]. However, the majority of recent reports found that this factor was not an independent predictor of survival. In particular, there was no significant difference in survival probability between patients undergoing en-bloc resection of one organ and those who had two or five resected organs. As in other series, those reports concluded that the involvement of several organs should not be an absolute contraindication for extended surgery [2, 5, 25].

## 17.9 Lymph Node Involvement and Tumor Dimension

The presence and extent of lymph node metastasis and tumor dimension are the most powerful determinants of survival following R0 resection. In the GIRCG study, Pacelli et al. [3] demonstrated that nodal status was an independent prognostic factor at multivariate analysis while the T dimension was confirmed only in univariate analysis.

The study of Martin et al. [1], in which only patients who underwent R0 resection were considered, showed that nodal status and T status were independent prognostic factors at multivariate analysis, whereas tumor size was a negative prognostic factor only in univariate analysis.

Along the same lines, other authors [7, 10] confirmed the prognostic power of lymph node metastatic involvement and added roles for tumor diameter and infiltration pattern.

Finally, the importance of lymph node involvement has been reported in almost all studies, demonstrating the negative power of positive nodal status (N+) [1, 2, 18], number of lymph nodes involved [3, 7], or extensive lymph node spread (N3+) [5].

## 17.10 Neoadjuvant Approach

In consideration of the prognostic impact of radical resection in cT4b forms, and in light of the results of randomized trials on neoadjuvant chemotherapy in locally advanced GC, the option to subject these patients to induction

chemotherapy has been investigated in recent years. Although no randomized trials are currently available, some retrospective or observational experiences suggest that these treatments may be associated with high R0 resection rates and long-term survival in responding cases [28, 29]. The addition of taxanes and targeted therapies to chemotherapic regimens provided further improvements to such results [30, 31].

## 17.11 Multimodality Treatments

Locoregional and peritoneal recurrences represent the main pattern of failure in locally advanced GC, even after a potentially R0 resection. To achieve better local and peritoneal control of the disease, the addition of intraperitoneal locoregional treatments, such as HIPEC (hyperthermic intraperitoneal chemotherapy), has been proposed in some selected cases [32]. To date, no high-quality studies in this specific setting are available in the literature; however, the strong rationale of the combination of neoadjuvant and locoregional treatments deserves further investigation in well-designed prospective trials. In Fig. 17.2, a proposed therapeutic approach to cT4b gastric cancer is presented.

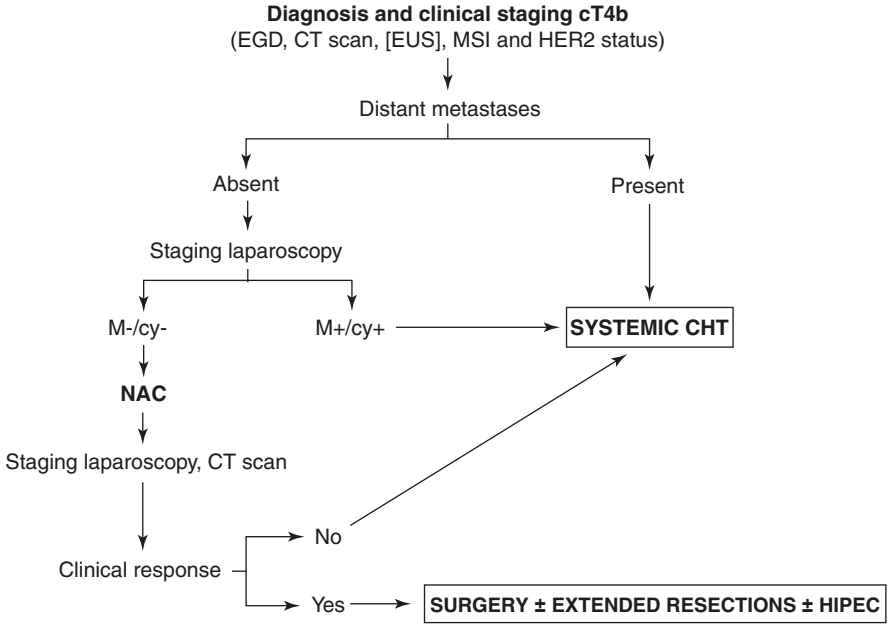


**Fig. 17.2** Proposed therapeutic approach to cT4b gastric cancer. *EGD* esophagogastroduodenoscopy, *CT* computed tomography, *EUS* endoscopic ultrasonography, *MSI* microsatellite instability, *CHT* chemotherapy, *NAC* neoadjuvant chemotherapy, *HIPEC* hyperthermic intraperitoneal chemotherapy

## 17.12 Conclusions

In summary, patients with locally advanced gastric cancer may require multivisceral resection to achieve disease clearance and negative resection margins. Patients' good performance status, absence or low number of clinically positive regional lymph nodes, and the possibility to perform a complete resection are associated with improved early and late outcome. Staging laparoscopy with peritoneal washing is advisable to exclude peritoneal metastases and confirm the involvement of adjacent organs. Neoadjuvant chemotherapy in clinically fit patients may be associated with tumor downstaging and higher possibility of R0 resection. The addition of HIPEC or other locoregional treatments may represent a new frontier to improve the prognosis in these advanced forms.

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# Surgical Treatment in Elderly Patients

# 18

Stefano Rausei, Federica Galli, and Angelo Benevento

## 18.1 Introduction

Stomach cancer mostly affects older people and the world's population is aging. These are the unquestionable assumptions of this chapter.

It is well known that the progressive demographic evolutions are changing the world's population, with a direct increase of the global burden of cancer [1]. Gastric cancer (GC) in 2020 caused more than 1,000,000 new cases (6% of all cancers): the doubling of the number of people aged 60 years and older expected over the next two decades will induce a relevant increase of GC cases (+101% with more than 930,000 new cases specifically expected in people aged >70 years) [2]. The demographic effect strongly overcomes the well-known "birth cohort effect" associated with the significant reduction of GC rate among the next generations related to the reduced exposure to risk factors (e.g., *Helicobacter pylori* infection).

Therefore, although there is substantial evidence of a declining GC incidence [3], the management of GC in older patients will remain a growing challenge for clinicians and surgeons.

Particularly, comorbidities and age-related frailties make it difficult to diagnose and treat GC according to individual tolerance [4]. Guidelines do not include specific recommendations for the elderly population because patients >70 years old are often excluded from randomized studies [5].

It is definitely clear that the treatment of GC in older people needs multidimensional knowledge of the patient and his disease with a developing awareness about new clinical and surgical approaches, basic endpoints (i.e., quality of life), and economic considerations.

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## 18.2 Aging and Frailty

The world's population is aging and this represents the most relevant social transformation of the current and future centuries, with direct implications for all society's sectors. In fact, since older persons are increasingly seen as effective resources for social development, globally there is no place for any stereotyped ageism [6]. The increasing concerns about their well-being impose increasing pressure on public healthcare systems. Hence, consistently with the actions identified by the World Health Organization (WHO) for the "Healthy Ageing" program [7], a cancer diagnosis in an elderly subject can no longer imply "simple" support therapy for symptom relief. It needs to be carefully assessed according to tumor- and patient-related therapeutic possibilities. In fact, in older people the onset of a new severe disease (such as cancer) suddenly alters the multifaceted and continuous passage among physiological changes and chronic multimorbidities: the understanding of the basic state of equilibrium of each elderly woman/man allows these possibilities to be verified and "measured", regardless of her/his year of birth.

### 18.2.1 Definitions

The introduction of categorical definitions of the old, elderly, aged and aging has always been difficult and not widely applicable. The chronological criteria already proposed by the United Nations in 1999 [8] defined people over the age of 60 as "elderly" and distinguished "oldest-old", that is, persons aged 80 years or over. In the same period, the WHO shifted the cut-off for "elderly" to 65 years, recognizing the same category for octogenarians [9]. Since then, other proposals with different cut-offs have been advanced that introduced new age-related categories (i.e., "young old", "middle old", and "very old" or "old-old"). However, these classifications attempted to respond to sterile taxonomic needs, without any significant implication for clinical practice.

The assumption of a dynamic understanding of any specific geriatric situation is the concept of frailty (not age *per se*). Frailty has been defined as the "progressive age-related decline in physiological systems that results in decreased reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes" [7, 10]. Although care dependence and comorbidities represent different aspects of aging, frailty is strictly associated with them in terms of both correlation and numbers (for comparable crossmatch rates) [11]. Frailty is not so easy to be measured and there is great uncertainty about its frequency. However, some of its general patterns have been reported: the prevalence of frailty rises with age and is higher in women, in lower socioeconomic groups, and in ethnic minorities [12]. Interestingly, since psychosocial factors play a relevant role in frailty development, frailty is not a static feature, but is a dynamic process, implying fluctuations between states of different severity. In other words, the course of frailty varies strongly from individual to individual and seems to be reversible. Therefore, comprehensive geriatric assessments with person-tailored interventions

can prevent negative health-related outcomes. When surgery is mandatory for treatment, prevention means stressing prehabilitation programs for perioperative care [13].

### 18.2.2 Indexes and Scores

In order to offer more patient-tailored care, clinicians need adequate tools to assess frailty degrees in daily practice. With this purpose, two aspects of the life of older people have been recently explored: the physical phenotype, as the result of the accumulation of age-related deficits, and the comorbidities, as the total burden of chronic diseases. Based on these (different but complementary) aspects, several score systems have been proposed. The two most widespread models are the Clinical Frailty Scale (CFS) for the physical phenotype [14] and the Charlson Comorbidity Index (CCI) for comorbidities [15]. Even recently, both these score systems showed a relevant prognostic role after GC surgery.

## 18.3 Surgical Outcomes in Elderly Patients

It is well known that elderly patients experience significantly greater morbidity and mortality after surgery. This evidence is also true for GC: mortality rates after gastrectomy can reach 8% in older people [16, 17]. At the moment, there is no systematic use (or prospective validation) of frailty and comorbidity scores supporting this evidence. However, several retrospective series showed that postoperative complications decrease in elderly patients with low frailty/comorbidity indexes [18, 19]. Undoubtedly, advances in anesthesiologic and surgical techniques have improved short-term outcomes in elderly patients. However, the operative procedure to be used in such patients should be carefully selected. Despite the GC treatment guidelines [20], sometimes a “non-operative” approach or a “limited” surgery could be chosen to prevent poor outcomes.

### 18.3.1 Extended Lymphadenectomy

Gastrectomy with D2 lymphadenectomy is considered the gold standard in the treatment of advanced resectable GC, without any exception regarding age or comorbidities [20, 21]. Nonetheless, several observational studies demonstrated that the category of elderly/high-risk patients (with its less aggressive tumors) often induced surgeons to use a less aggressive approach, with particular regard to the extent of lymphadenectomy [22]. In Western countries previous controversial results led to resistance against extended lymphadenectomy, focusing on the relevant postoperative complication rates, particularly in older people. More recent reports have confirmed the prognostic role of D2 nodal dissection [23], but when lymphadenectomy was analyzed in elderly patients significant benefits remained

only for disease-specific survival and not for overall survival. The non-negligible complication rates following D2 gastrectomy in high-risk elderly patients (close to 40% in patients with CCI >5) have been considered the likely cause of this survival discrepancy. This hypothesis was valid for early GC as well as for locally advanced disease.

Therefore, considering short-term outcomes and their direct implications on survival, in older high-risk patients a limited nodal dissection should be considered.

### 18.3.2 Minimally Invasive Surgery

Recently, the KLASS-02 trial demonstrated that the laparoscopic approach reduces complication rates after D2 distal gastrectomy [24] even for locally advanced GC. Nonetheless, specific analysis according to age was not performed and patients aged 80 and older were excluded from this study. Considering several Eastern experiences on laparoscopic gastrectomy in elderly patients, two meta-analyses concluded that it is a safe procedure [25, 26]. More recent studies (always from Eastern countries) confirmed this result, even in the oldest-old population [27].

Elderly patients with GC could benefit from surgery modulated in terms of reduction of both the extent of resection and surgical trauma. It is well demonstrated that minimally invasive surgery ensures less trauma than open surgery (with similar survival results). The advantages in terms of quicker recovery reported for laparoscopic distal gastrectomy in elderly patients are proof of this.

### 18.3.3 Palliation

Many GCs are diagnosed when the tumor is not curable. This is even more evident in elderly population. Thus, the need for palliation of a bleeding or obstructing tumor in frail people is not a rare possibility. However, there are no relevant studies clarifying when and how to palliate these GC cases.

For this specific setting of patients, the ineffectiveness of palliative gastrectomy in terms of long-term survival must be stressed [28]: more recently, an analysis conducted on a SEER (Surveillance, Epidemiology, and End Results) series of over 6000 cases including almost 3000 elderly patients has verified that any slight survival benefit after palliative gastrectomy in stage IV GC was substantially nullified in people aged 66 or older [29]. These results are also consistent with the most recent evidence acquired in the field of palliative medicine [30].

Nonetheless, potentially the improvement in quality of life could result in increased survival due to relief of obstruction and chronic bleeding and recovery of an adequate nutritional state. It is clear that palliative surgery should be considered only if there are no alternative (endoscopic/radiologic) solutions.

Specifically, if total gastrectomy is not accepted as palliative treatment owing to the risks of unacceptable postoperative morbidity, gastric resection represents a more careful and effective palliation (even when compared with tumor bypass

procedures) [31]. Palliation of bowel occlusion due to peritoneal carcinomatosis by bowel bypass generally is not recommended.

## 18.4 From Indication to Perioperative Management

Surgical morbidity in GC surgery is reported to be high (over 30%) [23]. Postoperative complications are obviously associated with postoperative mortality but also result in a well-known detrimental effect on long-term survival [32]. This aspect has a wider relevance in the elderly. Therefore, it is mandatory to prevent morbidity and mortality after surgery, especially in this population. As specified above, sometimes preventing morbidity could imply avoiding a surgical procedure in a particularly frail/high-risk patient. More often, it implies modulating surgery according to the patients' frailties and risks. The preoperative work-up represents the time to assess these risks. In this regard, it is to note that nutritional status (and sarcopenia as a measure of the decrease of muscle tissue) is a primary parameter to consider in elderly patients, along with frailty and comorbidity. The rate of malnutrition in GC patients is exaggeratedly high (85%) [33], and interestingly is very similar to those of the general geriatric population [34]: some cumulative effects of the prevalence of malnutrition in elderly GC patients are to be expected.

Prevention means to know, understand, and anticipate the problems. The knowledge and understanding of geriatric problems necessarily need a multidimensional evaluation of the patient; their anticipation needs solutions for prevention.

### 18.4.1 Multidimensional Evaluation and Enhanced Recovery After Surgery

All the centers devoted to surgical oncology have a multidisciplinary team in order to discuss and plan specific stage-adapted therapeutic strategies for every patient. Especially for elderly/frail patients, the treatment strategy must be patient-tailored rather than stage-adapted. In fact, before defining the best therapeutic options for the tumor, in these cases the best therapeutic options for the patient are to be defined. Hence, for the purpose of an exhaustive multidimensional assessment, the multidisciplinary team should also include a geriatrician, an anesthesiologist, a nutritionist, and—last but not least—a psychologist.

The aim is to modulate the treatment according to the patient's real tolerance and recovery possibilities. In fact, since frailty is a dynamic process, its improvement is not to be excluded *a priori*: prehabilitation seems to result in significant improvement in physical status among patients undergoing surgery for GC [35], but further investigation is required to determine any effect on overall oncologic outcomes and in the setting of the elderly patient.

The Enhanced Recovery After Surgery (ERAS) principles have also been suggested for the perioperative management of GC [36]; the validity of the ERAS items has been verified in several clinical experiences, some of which performed on

elderly populations. It seems that older GC patients show very high compliance rates with the ERAS program [37], with efficacy even after total gastrectomy [38]. Nonetheless, after reaching the ERAS discharge criteria, older and frail patients often require rehabilitation with additional nutritional support before they return to their ordinary life. These patients are usually transferred to chronic hospitals for these therapies. Once again, the use of frailty and comorbidity scores was suggested to predict non-home discharge in order to decide on an adequate therapeutic strategy after surgery [39].

## 18.5 Conclusions

Stomach cancer mostly affects older people and the world's population is aging. To these assumptions, this chapter added further unquestionable evidence: GC surgery is risky for elderly patients.

The optimal treatment for older people affected by GC should be defined on a patient-by-patient approach, carefully considering frailty, comorbidities, tumor symptoms (and tumor progression), and the patients'and their family's priorities with the potential changes induced by surgery on the patient's care.

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# Palliative and Emergency Surgery in Gastric Cancer

19

Elena Orsenigo and Maria Bencivenga

## 19.1 Introduction

Gastric cancer (GC) is the third leading cause of cancer death worldwide [1]. Beyond the oncological problems related to the cancer, patients often present symptoms due to perforation, overt bleeding or gastric outlet obstruction. The clinical implications of these conditions on the outcome of gastric carcinoma are difficult to determine because the definitions used are imprecise or not stated [2, 3]. Today, in complicated gastric cancer (CGC) the most important issue is to identify the cases candidate to surgery (radical or palliative) or other treatments. These situations and the respective treatments are summarized in Fig. 19.1 and detailed in the text below.

## 19.2 Gastric Cancer with Outlet Obstruction

Gastric outlet obstruction (GOO) is defined as a blockage of the distal stomach or duodenum. It reduces quality of life and patients present various symptoms due to the cancer progression such as nausea, vomiting, regurgitation, poor oral intake, and malnutrition. Successful treatment of GOO is necessary both for patients scheduled for perioperative therapy and for those with stage IV disease who only require best supportive care. Until the development of endoscopic procedures, surgery was the only treatment of these patients. Today, however, many options, both surgical and endoscopic, are available to treat these patients. It is difficult to establish which

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| | | Type of emergency | | |
|---|---|---|---|---|
| | | **Occlusion** | **Bleeding** | **Perforation** |
| **Gastric cancer stage** | **Resectable** | **N0**: Upfront surgery<br>**N+**: LPS + feeding jejunostomy *or* decompressive gastrostomy | **N0**: Endoscopic hemostasis *and then* upfront surgery<br>**N+**: Endoscopic hemostasis *to allow* chemotherapy | **R0 Resection** (*consider*: two-stage radical gastrectomy in case of hemodynamic instability) |
| | **Unresectable and stage IV** | **< 6 months***: SEMS<br>**> 6 months****: GJ, EUS-GE | **Palliative therapies** (endoscopic, embolization, radiotherapy)<br>**Surgery** only in case of unsuccess | **Palliative gastrectomy** |

**Fig. 19.1** Summary of emergency and palliative treatments in gastric cancer. *SEMS* self-expandable metallic stent, *EUS-GE* endoscopic ultrasound-guided gastroenterostomy

patients will benefit from upfront resection; only accurate clinical staging can determine the optimal treatment for the patient. Moreover, patients suffering from this condition often present intractable vomiting and severe malnutrition, which further compromise the outcome.

Based on the clinical stage, it is mandatory to distinguish between

– resectable GC and
– unresectable/stage IV GC

and subject the patient to a tailored treatment.

### 19.2.1 Palliation for Unresectable/Stage IV Gastric Cancer with Outlet Obstruction

Today there are several treatment options to alleviate GOO in untreatable GC: endoscopic stent insertion, endoscopic gastrojejunostomy (GJ), gastric partitioning combined with gastrojejunostomy (open or laparoscopic), surgical traditional GJ, and reduction surgery. Previous studies revealed that endoscopic stenting may be reserved for physically deteriorated patients with shorter life expectancy and surgical GJ for those with a good performance status [4–7]. Unfortunately, it is not clear which treatment will be more effective for patients with unresectable/stage IV GC complicated by GOO. The recent American Society for Gastrointestinal Endoscopy guideline provides evidence-based recommendations for the endoscopic management of GOO [8]. These include a comparison of GJ to the placement of self-expandable metallic stents (SEMS) and covered versus uncovered SEMS. In patients with incurable malignant GOO undergoing a palliative procedure, they suggest either SEMS placement or surgical GJ. Based on shared decision-making, in patients not eligible for radical surgery, with short life expectancy (<6 months), in order to quickly restore oral feeding and achieve a short recovery, SEMS placement is

suggested. Instead, in patients with a life expectancy >6 months and good performance status, surgical GJ is preferred. Unfortunately, we have to take into account that SEMS may decrease the interval before starting chemotherapy, but it has a higher reintervention rate compared with GJ. In these guidelines endoscopic ultrasound-guided gastroenterostomy (EUS-GE) with lumen-apposing metal stent (LAMS) was considered an off-label use. This new technique has been associated with more favorable short-term outcomes, including low complication rates and shorter time to restart oral feeding, but it has a higher rate of stent obstruction requiring repeated endoscopic treatment [9–11]. Tonozuka et al. describe the current status and perspective of EUS-GE concluding that this procedure has a higher initial clinical success rate and a lower failure rate requiring intervention compared to SEMS [12]. Fan et al., in a recent meta-analysis, analyzed the clinical outcomes of EUS-GE in terms of technical and clinical success and complications and they concluded that, although EUS-GE and GJ have similar clinical success rates, EUS-GE has a lower complication rate. EUS-GE seems to be a safe, effective, and minimally invasive choice for patients with GOO [13]. Moreover, Antonelli et al., in their meta-analysis, conclude that EUS-GE has a high rate of technical and clinical success when performed in expert centers and appears to be relatively safe, representing a non-inferior minimally invasive alternative to surgery. Nevertheless, the paucity of long-term clinical outcomes suggests prudency and a need for further research [14]. Finally, EUS-GE appears as a promising alternative to GJ or SEMS. While the clinical outcomes of GJ, SEMS, and EUS-GE are comparable, we have to consider that endoscopic procedures are associated with shorter length of hospitalization stay. Moreover, delayed gastric emptying is an adverse event of GJ, with an overall incidence of 10–26% of cases [7]. In order to improve function of GJ, a modified GJ with stomach partitioning has been proposed [2, 7, 15, 16].

Finally, another option could be reduction surgery defined as gastrectomy performed for patients with incurable factors (unresectable liver and peritoneal metastasis), with tumor-associated symptoms such as bleeding and obstruction [17]. Nevertheless, an international cooperative randomized controlled trial failed to demonstrate any improvement in patients' survival of reduction surgery [18]. For this reason, there is a strong contraindication to perform this type of surgery.

In conclusion, the management of GOO in unresectable/stage IV GC may be decided after a multidisciplinary evaluation of patients' performance status, in order to define if they are fit for chemotherapy, and taking into account the expertise of the physicians and center.

### 19.2.2 Radical Surgery in Gastric Cancer with Outlet Obstruction

Almost 7% of patients with GC presents GOO, with a wide spectrum of symptoms and signs. They could have signs of hypovolemia, due to repeat vomiting, various electrolyte imbalances and marked dilatation and edematous thickening of the gastric walls. Moreover, malnutrition is very common in GC patients and can be detected in up to 85% of patients. Malnutrition is associated with increased

morbidity and mortality, prolonged hospital stay, poor treatment tolerance, and lower survival rate [18–20]. In patients with resectable GC presenting with GOO, it is important, first of all, to solve the obstruction. Then, it is possible to consider a radical surgery with adequate node dissection. Initial treatment should consist of fluid administration to correct any electrolyte abnormalities, and gastric decompression by positioning a nasogastric tube. Then, we have to consider the treatment options for managing both GOO and GC. If there are no suspicious nodes on accurate staging, upfront surgery can be considered. According to Japanese Gastric Cancer Treatment guidelines 2018 (fifth edition), gastric resection and D2 lymphadenectomy should be performed [17]. If suspicious nodes are detected on staging examinations, neoadjuvant chemotherapy represents the gold standard, so the first aim is to solve the GOO with different strategies (SEMS, surgical resection, decompressive gastrostomy and feeding GJ). An upfront surgical resection may be an option, but we have to consider that a significant portion of patients with GOO (58.2%) underwent non-curative surgery because the tumors are large, with a high rate of perineural invasion, undifferentiated tumor histology and infiltrative gross types [21]. For this reason, it is important to have the conditions to start chemotherapy. The use of SEMS is principally indicated in untreatable or stage IV GC with a short life expectancy and rarely as a bridge to radical surgery. In patients with GOO candidate to chemotherapy, we can consider the possibility of performing staging laparoscopy to place a feeding jejunostomy and, when necessary, a decompressive gastrostomy. These procedures can allow patients to complete the neoadjuvant therapy while improving their nutritional status. Moreover, considering that the rate of peritoneal metastases ranges from 15% to 59% of patients with GC and GOO [22–24], laparoscopy can relieve previously undetected implants.

## 19.3 Gastric Cancer with Overt Bleeding

GC bleeding occurs in the 58% of bleeding cases from upper gastrointestinal malignancies [25]. It has been estimated that 1–10% of hospitalized GC patients initially present with overt bleeding (OB) [26]. However, gastric malignancies represent a very small fraction of upper gastrointestinal bleeding events, about 2–8% of all cases [27]. The causes of most upper gastrointestinal bleeding cases in oncological patients seems to be the same as in the general population, such as peptic ulcers, esophageal and gastric varices, esophagitis and erosive lesions [28]. OB directly occurs from the tumor in 2.9% to 4% of all cases [29], whereas minor bleeding is a well-known characteristic of GC, often causing chronic microcytic hypochromic anemia. Urgent esophagogastroscopy is the first examination used to establish the diagnosis, stratify the risk and treat the bleeding. Endoscopy represents a faster, safer, and minimally invasive alternative to surgery. The initial hemostasis rate has been described as 75% of the cases. However, bleeding from a tumor is difficult to treat and recurrent bleeding events are frequent after successful hemostasis. The most useful device is the Coagrasper hemostatic forceps that delivers targeted monopolar coagulation to the precise site of bleeding.

In cases of unresectable/stage IV GC with OB, we have to consider palliative therapies, such as hemostatic drugs, endoscopic therapy, emergent embolization by interventional radiology and radiotherapy. If endoscopic bleeding control therapy fails, selective embolization of the bleeding artery could be an option, considering emergency palliative surgery only in cases of unsuccessful hemostasis. Palliative short-course radiotherapy is an effective treatment that can provide durable palliation of bleeding, but it is usually reserved for when the cause of bleeding has been stabilized [30]. In cases of resectable GC, the aim is to control the OB and, after a multidisciplinary discussion, to direct node-negative patients to upfront radical surgery and consider node-positive patients for neoadjuvant chemotherapy. Surgically treated GC patients with OB seem to demonstrate poorer outcomes compared to those treated before surgery with successful endoscopic hemostasis [27]. Nevertheless, Wang et al. revealed that GC with OB is not synonymous of advanced GC, and its prognosis is no worse than that of GC without OB. In their study, patients with proximal GC with OB had less advanced pathological stages and a better prognosis than patients with proximal GC without OB [31].

## 19.4 Perforated Gastric Cancer

Perforated GC is a very rare condition with an incidence ranging from 0.5% to 3.9% [32]. Although the diagnosis of a perforation can be normally achieved, differentiation between a malignant and benign etiology remains difficult. Obviously, it is easier in patients with a known history of GC. Although rarely, it has been described that gastric perforation can be caused by chemotherapy or chemotherapy combined with targeted therapy [33, 34]. It is crucial to distinguish between benign or malignant disease and between resectable and unresectable/stage IV GC. Frequently the perforated GC is not diagnosed preoperatively. The diagnosis is mainly based on clinical presentation. Plain abdominal x-rays (erect) may reveal dilated and edematous intestines with pneumoperitoneum and the computed tomography scan can demonstrate a suspected GC. Management of perforated GC is not well established and there are no clinical guidelines supporting a specific treatment algorithm in these patients. Treatment depends on the knowledge of diagnosis, the level of peritoneal contamination, hemodynamic instability and the presence of metastases at exploration. There is no doubt that peritonitis requires an emergency surgical treatment but there are some scenarios that can be found intraoperatively that could influence the decision.

In the case of serious hemodynamic instability some authors suggest the concept of damage control surgery instead of an immediate gastrectomy and that two-stage gastrectomy can decrease postoperative mortality rates and improve long-term survival [35]. One-stage gastrectomy was found to be associated with high mortality rates (0–50%) [36]. The outcome after emergency surgery in patients with free perforation depends on the stage of the disease and whether a curative resection could be performed. The two most important issues for perforated GC are to achieve radical R0 resection, regardless of whether the surgical approach is a one-stage or

two-stage gastrectomy, and to resolve the peritonitis. When radical curative surgery is feasible it would be performed according to the guidelines of the Japanese Gastric Cancer Association [19]. If curative R0 resection cannot be expected due to hemodynamic instability, it is recommended to avoid palliative gastrectomy and firstly treat only for the peritonitis. On the contrary, in cases of unresectable/stage IV GC a palliative resection seems to be superior to simple closure or omental patch [37, 38].

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# Evolving Concepts in the Treatment of Stage IV Gastric Cancer

20

Stefano Cascinu

Gastric cancer is the fifth most frequent cancer and the third leading cause of cancer death worldwide. Most gastric cancer patients are advanced at diagnosis and nearly half of resected patients have a recurrence [1]. Their outcome is poor with a median survival not exceeding 10–16 months and the only effective treatment is systemic therapy. In this chapter we discuss the available data on the systemic treatment of advanced gastric cancer and how they could be used in clinical practice.

## 20.1 The Evolving Role of Systemic Treatment

In the 80s it was clearly shown that combination chemotherapy can prolong survival and improve quality of life but, unfortunately, in spite of the availability of always more active cytotoxic drugs, median survival has plateaued at 9–11 months [2]. This is why an "old" regimen such as the platinum/fluoropyrimidine doublet continues to be the preferred backbone of first-line treatment. Since it has been shown that oxaliplatin and capecitabine can safely replace cisplatin and 5-FU, FOLFOX or XELOX are the most commonly used worldwide [3]. A valuable first-line alternative in patients intolerant to platinum analogs can be FOLFIRI (5-FU, folinic acid, irinotecan), which is effective and well tolerated [4]. The role of a third cytotoxic (docetaxel or epirubicin) added to doublet chemotherapy has been investigated and debated for years. Indeed, both docetaxel and epirubicin-containing triplets yield higher response rates but with more severe toxicities [1].

Similarly to other gastrointestinal tumors, targeted therapies were investigated in the treatment of gastric cancer. However, apart from HER-2 positive tumors, representing no more than 10–15% of gastric cancers, where trastuzumab improved the outcome of patients, no other agents were found effective [5].

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In recent years, immunotherapy with immune checkpoint inhibitors has revolutionized the treatment of many cancers. One of the most relevant immune checkpoints is programmed death-1 (PD-1), a negative costimulatory receptor expressed mainly on activated T cells. Its overexpression has been observed in gastric cancer, making PD-1 pathway inhibition a therapeutic target. The first trial including gastric cancer was the KEYNOTE-012 study. The following phase 2 study, KEYNOTE-059, assessed the safety and efficacy of pembrolizumab in gastric cancer. Based on its results, the FDA granted approval for pembrolizumab in advanced gastric cancer expressing PD-L1 and progressing on or after two or more systemic therapies. However, in the phase 3 trial KEYNOTE-061, pembrolizumab did not demonstrate a significant improvement in survival compared to paclitaxel in second-line therapy. Although these conflicting results make it difficult to define the role of immunotherapy in clinical practice, retrospective analyses showed that pembrolizumab and nivolumab are highly effective in microsatellite instability and Epstein-Barr virus (EBV) tumors, suggesting a role in these specific subgroups of patients. The attempts to move pembrolizumab and nivolumab to first-line treatment produced controversial results. In the KEYNOTE-062 trial, pembrolizumab proved to be noninferior in survival compared with chemotherapy. However, patients receiving chemotherapy had a better survival in the first 6 months of treatment, thus questioning the role of pembrolizumab in patients with more aggressive disease. Furthermore, improved survival was observed only in tumors with PD-L1 combined positive score > 10. This could allow one to select patients, but it was based on a retrospective analysis and the threshold was fixed without any relationship with biology. More recently, in the CHECK-MATE 649 trial, nivolumab in combination with chemotherapy (FOLFOX, CAPOX) resulted in a better survival (13.8 vs. 11.6 months). Similarly to pembrolizumab, it was effective in patients with a combined positive score > 5. Once again, this threshold is not related to biologic findings. Apart from patients with microsatellite instability-high (MSI-H) or EBV tumors, we should wait for further data to define the role of immunotherapy in gastric cancer patients [6].

## 20.2 From One Line to the Opportunity of Multiple Lines of Treatment

After a 20-year debate, the systemic treatment of gastric cancer moved from the role of first line to that of a second-line therapy. This was due to the disappointing results of trials in first-line chemotherapy as well as to the evidence of a progressive improvement in survival observed in patients receiving sequential lines of treatment. The proportion of patients who remain fit to receive further lines has grown from 20% to 51% for second-line therapy and from slightly above 0 to 25% for the third-line. Understanding of the nutritional issues in advanced gastric cancer patients

and the proactive interventions including nutritional counseling and early supportive care have resulted in better and safer delivery of second- and third-line therapies. At least three drugs, docetaxel, irinotecan and paclitaxel, improved survival in comparison with best supportive care. The strength of these data, in spite of the small sample sizes of the single trials, was that all achieved similar results in terms of efficacy and toxicity. Nevertheless, it was ramucirumab to change mostly the oncologists' attitude toward the management of advanced gastric cancer patients refractory to first-line chemotherapy. Ramucirumab, a monoclonal antibody inhibiting VEGFR-2, was effective in monotherapy (REGARD trial) or in combination with paclitaxel (RAINBOW trial). In monotherapy it achieved the same progression-free survival and survival as those observed in the trials with chemotherapy, with a more favorable toxicity profile. In combination with paclitaxel, ramucirumab obtained an impressive median survival of 9.3 months. It is worth recalling that this value is similar to that obtained in first-line therapy. Based on these data, ramucirumab in combination with paclitaxel is the standard of care for patients with a disease progression after a first line therapy not including taxanes. In patients previously receving taxanes, ramucirumab monotherapy may be effective and safe, sparing toxicity in comparison with chemotherapy [7]. The administration of later lines of therapy is clinically challenging because gastric cancer progresses rapidly in a short time. Physicians may miss the right time for switching to a subsequent therapy without careful follow-up visits. In order not to lose patients, we should remember that although progressive disease may be shown by radiological imaging, more often, the general conditions, clinical symptoms and tumor markers are the most important things to assess in order to switch therapy as early as possible. This is not relevant only for the step from the first to the second line but also from the second to the third line of treatment [7]. In fact, later line treatment has been embraced in both real world and trial settings. Some clinical experiences suggested that a third-line therapy may contribute to an improvement in survival. However, it was the TAGS trial that validated this strategy. This randomized phase III study compared the efficacy and safety of oral cytotoxic trifluridine/tipiracil chemotherapy with placebo in metastatic gastric cancer patients who had received at least two previous chemotherapy lines [8]. It significantly improved survival compared with placebo as well as time to deterioration of the Eastern Cooperative Oncology Group (ECOG) performance status score to 2 or higher. Moreover, it was safe with manageable neutropenia as the most frequent adverse event, making this drug an opportunity in this patient population with a great unmet medical need [9].

A relevant issue is the selection of a patient candidate to later lines. Probably, the factors able to predict a lack of benefit from a second-line therapy are performance status $\geq 2$, time to progression on the first line less than 6 months and peritoneal metastasis. More recently, malnutrition has attracted the attention of oncologists [10, 11]. Malnutrition is present in up to 80% of patients and, furthermore, it has been associated with an increased risk of developing treatment-related toxicities [12].

## 20.3 How to Further Improve the Outcome of Advanced Gastric Cancer Patients

It is undeniable that the improvement of outcome of advanced gastric cancer patients depends on the availability of effective drugs. Nevertheless, we should not forget that our skill in the management of patients in first line influences the clinical history of most patients in later lines. At least three different points may help us to design specific treatment strategies in order to offer the best approach for each patient. Advanced disease is not a homogenous disease. It includes two different situations: a locally advanced unresectable disease and metastatic disease. The prognosis is different. In locally advanced disease, median survival goes beyond 12 months, while it is only 6 months or less in metastatic disease. Also, the aim of treatment is different. In locally advanced unresectable disease we should pursue tumor shrinkage in order to make an unresectable disease resectable. This means that highly active regimens should be preferred. A three-drug regimen, like FLOT, may be a reasonable option. On the contrary, in the metastatic setting the aim of treatment is to improve survival and quality of life and, therefore, the treatment strategy is based on different lines of treatment. In reality, even the term "metastatic disease" does not define a homogeneous group of patients as it may include patients with oligometastatic disease or multiorgan metastatic disease. The definition of oligometastatic disease is still debated [13, 14]. Probably we should include within this term all the patients with a radically resectable metastatic disease. Nevertheless, these patients should not undergo upfront surgery but only after a response to or long-lasting stable disease on systemic treatment. Once again, the question is which is the best regimen. In a retrospective analysis, the FLOT regimen seems to be an appropriate option even if we have to wait for the prospective randomized trial.

Another crucial aspect is how long to continue treatment. In the case of a clinical response or stable disease, can we discontinue therapy waiting for a progression before restarting treatment? It is not clear. Chemotherapy prolongation until disease progression is the standard of care on the basis of published international guidelines and randomized phase III clinical trials. Nevertheless, this strategy is consistently associated with cumulative toxicity and prompt development of drug resistance, with disease progression after 4–6 cycles. The cumulative toxicity rate with continued administration of chemotherapy could also negatively affect the patients' quality of life. This reinforces the need to extend the time to progression in the subgroup of patients with a responsive disease. A reasonable strategy could be deintensification, withdrawing cisplatin or oxaliplatin. Probably we should individualize the approach, carefully assessing patients in treatment vacation in order to do not miss performance status deterioration. It is undeniable that patients have achieved an improvement in survival over recent years and that this has been mainly due to a better treatment strategy. New treatments are urgently needed, but the greatest challenge will be to understand which cancer subgroup deserves a specific therapy and to design clinical trials tailored on these subgroups, in order to transfer the molecular classification acquisitions into clinical practice and to minimize the number of patients who receive a systemic treatment without any molecular selection.

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# Surgery for Stage IV Gastric Cancer: The New Edge

21

Paolo Morgagni, Maria Bencivenga, and Guido A. M. Tiberio

## 21.1 Introduction

Gastric cancer is diagnosed at stage IV in 35–55% of cases in Western countries [1] and median disease-specific survival in this stage is approximately 10 months [2], with overall 5-year survival estimated to be 3–5% [3, 4]. Based upon these epidemiological considerations, it appears important to establish therapeutic standards, but unfortunately it is difficult to conduct randomized trials in this heterogeneous group of patients and conclusive results may not be achieved for a long time. The results of the REGATTA trial [5] indicate that surgery should be avoided in stage IV gastric cancer. Indeed, palliative gastrectomy is much more invasive than chemotherapy and achieves similar survival results. However, in their trial, Fujitani et al. did not consider the possibility of a complete surgical resection of both gastric cancer and metastases, limiting their comparison to chemotherapy alone versus surgery only on the primary tumor plus chemotherapy.

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## 21.2 Is Surgery a Therapeutic Option?

Recent literature [6–14] shows that surgery, in particular if employed in the context of a multidisciplinary therapeutic strategy, may offer, at least to a selected subgroup of patients, unexpected results. Although the power of these studies is limited by their retrospective nature, they cannot be ignored.

Following the evolution of surgical management of metastatic colorectal cancer, surgery was at first considered for the management of hepatic metastases [6–10], on the theoretical assumption that hepatic metastasis may still characterize a regional and not a systemic disease, and thus display a better prognosis since the liver plays a "first-filter" role for the portal bloodstream. Unexpectedly, however, a recent Italian paper focusing on the surgical management of 287 stage IV gastric cancers [11] did not report better survival outcomes for patients with hepatic metastases when compared to those presenting metastatic disease in the peritoneal cavity, distant lymph nodes, extra-hepatic hematogenous locations or any possible combination of the above. The same paper also indicated that relevant 3-year survival rates of around 20% can be achieved, independently from the site of the metastasis, in the subgroup of patients who could benefit from a curative resection of both gastric primary and metastatic site. These important concepts are to be highlighted, as they reveal that a chance of effective treatment, if not of cure, should also be given to stage IV patients, instead of subjecting them to palliative chemotherapy or supportive care.

In the era of precision medicine and limited resources, the selection of candidates for an aggressive approach to stage IV gastric cancer gains particular relevance. This is even more true in the Western world, whose population cannot benefit from S1 chemotherapy regimens and where the curve which describes survival after multimodal treatment, including surgery, suffers a dramatic drop during the first year (40% mortality after 6 months and 60% 1 year after surgery).

The entire literature struggles in search of those clinical elements which could orientate patient selection and the therapeutic approach. A general consensus exists in identifying the possibility to achieve a radical (R0) resection both on the gastric primary and metastases as the most important clinical indicator. The clear survival advantage of curative R0 surgery over palliative R+ procedures is confirmation that integrated management including curative surgery offers unexpected results, at least to a selected subgroup of stage IV gastric cancer patients. Upon these findings, we consider that the REGATTA trial maintains its value for cases not candidate to curative R0 surgery, yet its conclusions should be at least discussed, if not completely rejected, when R0 resection is deemed possible.

Other prognostic indicators that emerge from the different published series concern the gastric primary and the histological type, but particular emphasis is given to the nodal status N of the TNM classification and to the extension of lymphectomy [11]; the prognostic role of the T staging of the gastric primary becomes clear when subgroups of R0 patients are considered. These variables also display a cumulative prognostic effect, and sustain the importance, especially when curative resection of

primary and metastasis is pursued, of adhering to surgical standards suggested for locally advanced gastric cancer, avoiding downscaling due to the advanced disease stage.

Metastasis-related variables display inconstant prognostic effect; they generally concentrate on the metastatic bulk (extension of peritoneal carcinomatosis, number and distribution of hepatic and lung metastases as well as of distant pathologic nodes), but also surgical peculiarities are taken in account such as, for example, the "simple" or "difficult" location inside the liver or the lung. it should be noted that in the cited Italian survey survival was unaffected by any of the considered metastasis-related variables.

The prognostic role of the lymphatic sphere in stage IV gastric cancer underlines and recalls the role of surgical technique, and the importance of high-quality surgery is further enhanced by the clear prognostic role played by curative R0 surgery, achieved both on the gastric primary and on metastasis. R0 resection is more likely to be obtained in patients with good performance status not requiring surgery in emergency conditions and must be pursued in referral centers by surgeons who closely adhere to common-sense guided surgical principles, capable of guaranteeing low mortality and morbidity rates. Indeed, the increase of the biologic cost of these procedures may easily hamper all possible efforts to improve patient prognosis.

In the quest for radicality, the extension of metastatic lesions plays a pivotal role. It is widely accepted that only the most favorable cases merit integrated aggressive management including surgery. However, there is no clear and systematic indication concerning the limits that define the surgical indication which is generally considered in case of limited carcinosis spots above the transverse colon (peritoneal cancer index [PCI] ≤6), 1 or 2 small (≤5 cm) hepatic metastasis in "easy" locations and involvement of posterior (station 12b and 13) or para-aortic (station 16a-b) nodes. These cases could be defined as "oligometastatic" gastric cancer. Of note, this definition should not include only the concept of disease burden but also that of response to chemotherapy: that of oligometastatic gastric cancer should be a dynamic definition (Fig. 21.1). Conversely, disseminated carcinosis, multiple and scattered hepatic metastases and mediastinal nodes represent clear contraindications [12, 13]. In such cases, surgery would be possible only in rare cases of extraordinary response to systemic chemotherapy, i.e., in those cases in which first-line therapy causes the disappearance of all the technical and/or the oncological factors of non-resectability. In these cases surgery will be aimed to the removal of only the residual disease: it is different from the R0 resection planned in oligometastatic cases, it does not take into account the initial volume and site of disease and this should be defined as "conversion surgery".

This concept of "conversion surgery" was first introduced in 2016 by Yoshida et al. [14] that proposed a new pragmatic and treatment-oriented classification of stage IV gastric cancer. They suggested distinguishing, among the cases of metastatic gastric cancer, four different biologic categories, according to the progressive increase of the metastatic burden (Fig. 21.2).

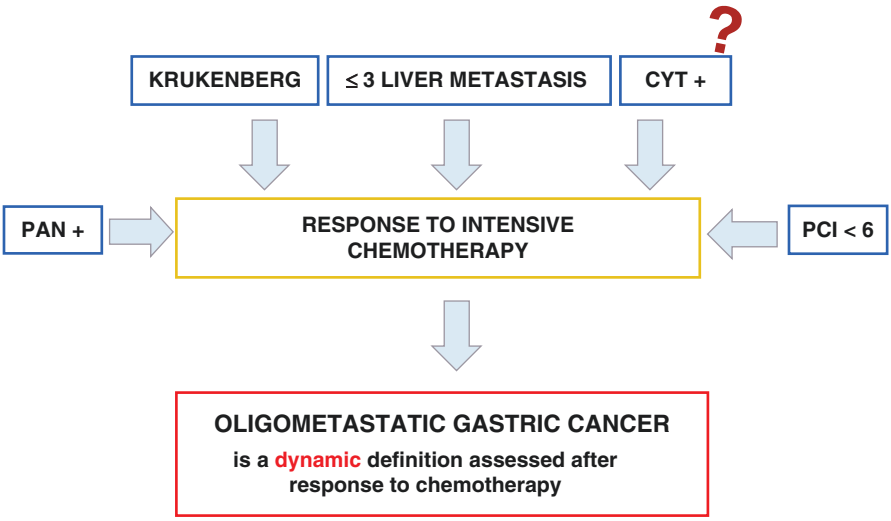


**Fig. 21.1** Dynamic definition of oligometastatic gastric cancer

## 21.3 Reappraisal of Yoshida's Classification

From the cultural perspective, conversion surgery is the new frontier in oncologic surgery. According to Yoshida et al., in all the cases included in categories 2 and 3, patients could undergo surgical treatment aiming at R0 surgery on residual disease after the conversion to resectability by a good response to chemotherapy. Conversely, an R0 resection on the whole initial tumor burden, either upfront or after "neoadjuvant" chemotherapy is indicated for tumors included in category 1, i.e., those cases who are deemed technically and oncologically resectable, although diagnosed at stage IV. This category 1 could be defined as the "oligometastatic" gastric cancer that we defined in the previous section. Of note, our proposed category of oligometastatic gastric cancer would include some cases that are in category 2 (the cases of limited, resectable liver metastases, i.e., two or three lesions in a single lobe, para-aortic lymphadenectomy at stations 16 a1 and b2) and category 3 (limited peritoneal carcinosis with PCI $\leq$ 6, synchronous mono- or bilateral Krukemberg) according to Yoshida (Fig. 21.2). In contrast with Yoshida's categories, some doubts exist regarding the inclusion of positive peritoneal cytology in the definition of "oligometastatic" (Fig. 21.3).

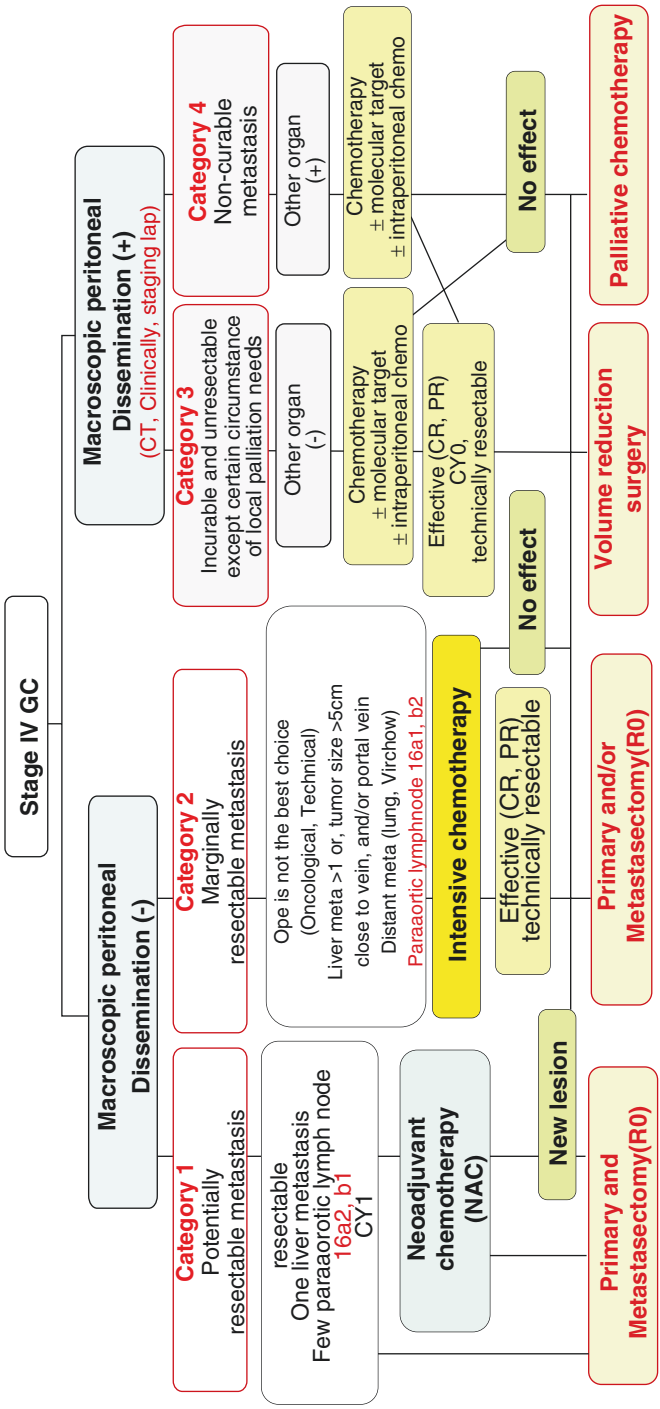


**Fig. 21.2** Yoshida's classification of stage IV gastric cancer. From [14] (published under the terms of the Creative Commons CC-BY license)

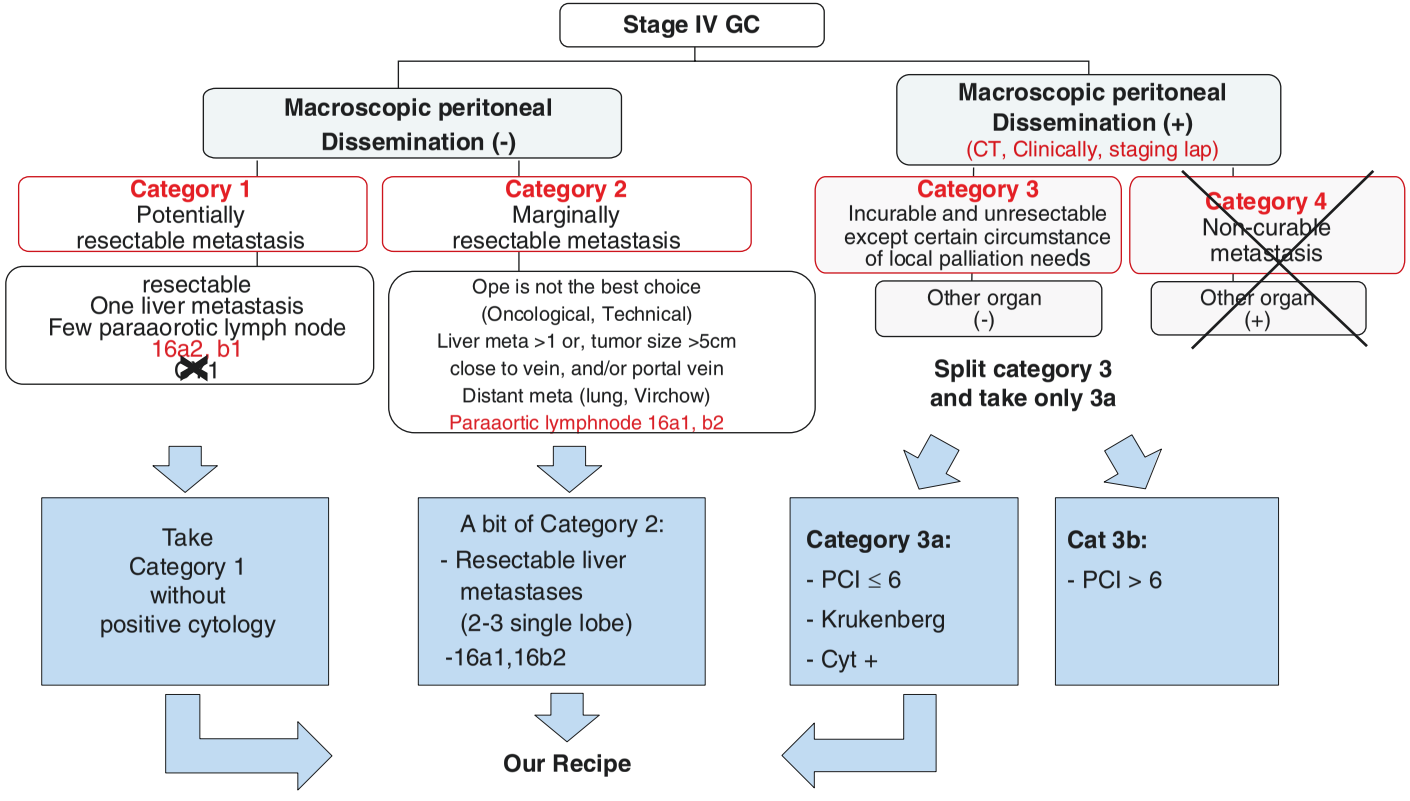


**Fig. 21.3** Our recipe of oligometastatic gastric cancer. Modified from [14] (published under the terms of the Creative Commons CC-BY license)

## 21.4 Timing of Restaging and Surgery in Oligometastatic and "Converted" Cases

The implementation of surgical indications in stage IV gastric cancer requires as a prerequisite the close collaboration between surgeons, oncologists and the multidisciplinary milieu that contribute to the best possible oncologic treatment, with particular reference to patient support.

Beside endoscopy and computed tomography, staging laparoscopy must be routinely employed in order to achieve the correct staging and restaging of the disease.

Other important issues are the type and duration of chemotherapy and the timing for surgery.

Interesting considerations could be made on these points based on the surprising results presented in some studies. In detail, a retrospective international cohort study, the CONVO-GC.1, which included data for 1206 patients subjected to chemotherapy and then to surgery and stratified according to the Yoshida categories, showed a median survival time after R0 resection of 49.1 months in category 1, 82.2 months in category 2, and 44.9 months in category 3 [15]. Of note, in category 3 no stratifications according to the burden of peritoneal involvement was made.

These surprising results, and especially the poor survival of patients in category 1 compared to category 2 and 3, indirectly suggest that upfront surgery or "neoadjuvant" schedules are not enough in stage IV patients, and as such both "oligometastatic" and "highly metastatic" patients should be treated with first-line intensive chemotherapy before surgery.

The type of drugs and the duration of chemotherapy should be selected in order to have the best objective response in a short time period in oligometastatic cases, then surgery will not be delayed if the restaging after 3–6 months shows response to treatment, while in highly metastatic cases, the schedule selection should consider the need to perform a second/third line of chemotherapy in most cases; conversion surgery may be hypothesized after at least 6 months of treatment; an interesting option could also be that of reducing the intensity of chemotherapy or even interrupt it for 2–3 months before surgery in these converted cases.

## 21.5 The Next Step: Choosing Oncologic Treatment on a Biologic Basis

The increasing efficacy of chemotherapy regimens and the introduction of target therapies and immune checkpoint blockade in the management of stage IV gastric cancer would likely expand the indications to conversion surgery. To date, only sporadic series of conversion surgery in highly metastatic patients after treatment with anti-HER2 agents [16] or immunotherapy [17] are available. As such, the benefit of surgery on residual disease in this context is unclear.

Another issue is whether to perform gastrectomy in cases of clinical complete responders. The collection of more evidence will provide stronger indications.

What is currently absolutely mandatory when a stage IV gastric tumor is diagnosed is the evaluation of the tumor's biological characteristics: this means performing at least immunohistochemistry for HER2, microsatellite instability (MSI) status (MLH1, MSH2, MSH6, PMS2), PD-L1 (evaluated as CPS that is the count of PD-L1-staining cells considering not only tumor cells but also lymphocytes and macrophages, divided by the total viable tumor cells ×100) [18] and the EBER-ISH (EBV-encoded small RNA in situ hybridization) analysis. This would pave the way to molecular-based treatments and to a definite prognostic improvement of this unfortunate category of patients.

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# Modern Therapeutic Approach to Peritoneal Carcinomatosis: Bidirectional, HIPEC, PIPAC

22

Annibale Donini and Daniele Marrelli

## 22.1 Introduction

Gastric cancer (GC) is the fourth most common cancer in the world with a 5-year survival rate of about 25%. During the follow-up, despite a macroscopically curative surgery (up to 40%), a large percentage of GC patients will develop peritoneal dissemination, which results in a less than 5% 5-year overall survival (OS) rate.

Instead, in primary GC, peritoneal metastases (PM) are a common finding seen in 5–20% of patients undergoing gastrectomy. Among advanced GC patients, peritoneal implantation is one of the most debilitating and common forms of metastases, in particular in patients affected by a serosal and diffuse histotype GC. For these patients, median OS is dramatically poor, 3–6 months without any treatment.

To date, specific treatments for peritoneal carcinomatosis are not so well defined [1].

Platinum or 5-FU-based regimens have been recommended as the first-line chemotherapy. Nonetheless, the 1-year OS rate is only 16–40.7% and the median survival is as short as 3.1–10.6 months, suggesting that the effect of systemic chemotherapy is limited.

Recently, conversion therapy combining induction chemotherapy followed by surgery seems to give promising results. Because it is difficult to extrapolate data about conversion therapy results to PM patients only, a subgroup analysis will be needed in the future.

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Others possible treatments include neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), cytoreductive surgery (CRS) and perioperative chemotherapy, which may include hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy.

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is an emerging option for PM treatment.

## 22.2 Bidirectional Therapy

Systemic chemotherapy alone for primary GC with PM is a disappointing not so beneficial plan of management. On the other hand, neoadjuvant chemotherapy can be modified for patients with peritoneal seeding by combining systemic and intraperitoneal chemotherapy, defined as bidirectional chemotherapy**.** Chemotherapy may gain access to small peritoneal cancer nodules via the systemic circulation and by diffusion from a chemotherapy solution within the peritoneal cavity.

Asian surgeons have recently proposed this treatment, which is associated with a high response rate and low toxicity. The treatment combines intraperitoneal administration of docetaxel and intravenous administration of 5-FU or oral administration of S-1. Japanese authors reported that such chemotherapeutic agent combinations, known to be effective for GC, could increase the rate of patients eligible for CRS and HIPEC procedures and potentially offer curative approaches with acceptable toxicity [2].

Yonemura et al. proposed a prospective phase II study that demonstrated the efficacy of the NIPS treatment. They stated that micrometastases in the peritoneal cavity should be reduced as much as possible before cytoreductive surgery, which remains the main key of treatment if a macroscopically curative resection (R0) could be achieved, using NIPS. Intraperitoneal chemotherapy was infused via an intrabdominal port and the macroscopic response to bidirectional chemotherapy was evaluated by laparoscopy. Compared to systemic chemotherapy, NIPS is a more powerful killer of tumor cells in intraperitoneal micrometastasis [3]. The micrometastases located outside of the surgically resected area must be eradicated immediately after CRS by HIPEC and early postoperative intraperitoneal chemotherapy.

Yonemura et al. reported excellent results but in particular in patients treated with curative surgery: median survival time, 5-year OS, and 10-year OS after complete cytoreduction were 20.5 months, 14.3%, and 8.3%, respectively. In contrast, all patients who received incomplete cytoreduction showed survival outcomes similar to systemic chemotherapy alone.

Pocard's group in France published in 2020 the first Western study that confirmed the feasibility and safety of bidirectional treatment using intraperitoneal and intravenous chemotherapy for patients with unresectable PM from GC, resulting in a 13-month median survival with limited morbidity. The decrease in peritoneal cancer index (PCI) after one bidirectional cycle is promising [4].

Bidirectional chemotherapy should be evaluated more extensively in phase I–II studies.

## 22.3 Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

HIPEC and CRS is already considered standard of care for selected patients with different gastrointestinal malignancies such as appendiceal tumors, peritoneal mesothelioma and colorectal cancer [5]. The combination of these two modalities takes advantage of surgery to remove all the visible tumor burden, and regional hyperthermic chemotherapy to kill free intraperitoneal cells and eradicate micrometastases. The HIPEC procedure consists of the intraperitoneal administration of chemotherapy drugs heated to a temperature greater than normal body temperature. Before HIPEC is administered, the surgeon usually performs the CRS, removing the primary tumor and the macroscopic peritoneal seeding. Secondly, either with an open abdomen and the Coliseum technique described by Sugarbaker in 1999 [6], or with a closed abdomen, HIPEC is performed, administering chemotherapics into the abdomen when a high temperature is reached.

HIPEC combines the pharmacokinetic advantage inherent to the intracavitary delivery of cytotoxic drugs, which results in regional dose intensification, with the direct cytotoxic effect of hyperthermia. A temperature between 39 and 43 °C enhances the chemosensitivity of tumor cells to the cytotoxic agents and increases their effectiveness, without achieving high plasmatic drug concentrations. The intraperitoneal drugs most commonly used in GC are: mitomycin c (15 mg/m$^2$) and cisplatin (50–200 mg/m$^2$), oxaliplatin (460 mg/m$^2$) and taxane (20–40 mg/m$^2$).

HIPEC administration has been described in different settings of the GC PM management.

### 22.3.1 Prophylactic Setting

Several Asian authors have reported a potential benefit from using intraperitoneal chemotherapy with or without hyperthermia, as a complement to curative surgery, in the absence of macroscopically evident carcinomatosis. HIPEC could play a role in the prevention of PM development in high-risk GC patients with peritoneal positive cytology and/or perforated tumors and/or affected by tumors with serosal involvement.

Based on Yan et al.'s meta-analysis [7], in which the use of HIPEC as an adjuvant treatment significantly improved the survival rates of GC patients, the GASTRO CHIP study, a multicenter European study is ongoing. In this study, T3–4 and/or N+ patients are randomized to neoadjuvant CT for 3 cycles, followed by gastrectomy vs. gastrectomy plus HIPEC with oxaliplatin. The final results are still awaited.

### 22.3.2 Therapeutic Setting

Even if there is an ongoing Dutch Trial (the PERISCOPE II), to date only Yang et al. [8] have provided the first phase III study regarding CRS and HIPEC in PM from GC. Median survival was 6.5 months after CRS as compared to 11 months in the CRS plus HIPEC group. There was similar morbidity between the two groups.

Glehen et al. [9] as well as Yang [8] suggested that HIPEC should be reserved only for patients with limited peritoneal carcinomatosis and when an R0 could be performed.

Knodelr et al. [10] evaluated a new therapeutic approach represented by the intraperitoneal administration of a trifunctional antibody, catumaxomab, characterized by the ability to bind to different antigens present both on the membranes of tumor cells (EpCAM) and T cells (CD3).

## 22.4 Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

PIPAC is a new surgical procedure used in selected patients affected by PM not suitable for CRS and HIPEC. Its objective is to alleviate symptoms, in particular to control ascites leading to a better quality of life, and to induce regression of the peritoneal dissemination. The first report of successful application of PIPAC in a GC patient was published in 2014. Since then, a number of papers have described the effectiveness and the safety of PIPAC in PM from various origins [11]. It is performed laparoscopically under general anesthesia. A pneumoperitoneum of 12 mmHg is induced; usually two other trocars are inserted. If ascites is present, it is completely evacuated by suction and quantified. PM according to the Sugarbaker score is evaluated. The micropump is installed into the 12 mm trocar and fixed under direct vision starting the chemotherapic intraperitoneal injection. The common drugs utilized are: cisplatin at a dosage of 7.5 mg/m$^2$ in 150 mL NaCl 0.9% and doxorubicin at 1.5 mg/m$^2$ body surface in 50 mL NaCl. The injection pump delivers the chemotherapy at a maximum pressure of 200 psi and a flow rate of 0.5 mL/min to the micropump. The fluid is therefore transformed to aerosol and applied to the abdominal surface for 30 min.

Recently Di Giorgio et al. [12] published a study in which 28 GC patients with PM underwent a bidirectional approach of PIPAC and intravenous chemotherapy. A pathological response was recorded in 61.5% of patients. The median OS was 12.3 months in the overall population and 15.0 months in patients undergoing more than one PIPAC procedure.

Also Alyami et al. [13] published a retrospective analysis of 42 patients affected by unresectable PM from GC treated with chemotherapy and PIPAC. All patients had systemic chemotherapy alternating with PIPAC. Overall, major complications (CTCAE—III, IV) occurred in only 10 (6.1%) and 5 procedures (3.1%), respectively. Median survival was 19.1 months. A total of 14.3% of patients became resectable and underwent curative-intent CRS and HIPEC.

We are awaiting results from the prospective, open, two-arm, randomized multicenter phase II clinical study PIPAC EstoK 01 that is evaluating the effects of PIPAC on patients with PM from GC with PCI >8, treated with systemic chemotherapy and two PIPAC procedures.

We can conclude that PIPAC can be regarded as a palliative procedure that could improve quality of life, or at least stabilize it from further deterioration. The following step will be to demonstrate if GC PIPAC could be used as a neoadjuvant procedure in patients with high PCI to conduct them to CRS. It seems that iterative PIPAC induces a regression of PM, but larger studies are needed to define the precise role of PIPAC in the management of PM from GC.

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# Siewert III Adenocarcinoma: Indications and Treatment

23

Andrea Zanoni, Simone Giacopuzzi, and Giovanni de Manzoni

## 23.1 Introduction

Siewert III are cancers of the proximal stomach invading the esophagogastric junction (EGJ), with tumor epicenter from 2 to 5 cm below the EGJ, according to the Siewert classification [1]. According to TNM 8th ed., they are considered gastric cancers [2]. Nonetheless, infiltration of distal esophagus makes them a separate entity. Siewert III cancer, although representing around 40% of EGJ cancers and being the EGJ cancer with the worst prognosis [3, 4], does not have a homogenous treatment [5–12]. The rationale for a separate discussion of this entity is the boundary position of this disease, which makes its biological and spreading behavior peculiar; consequently, treatment strategies must be distinctive, also in consideration of the surgical challenge.

## 23.2 Surgical Strategy

### 23.2.1 Indications According to Margins

Outcome after non-curative resections is poor and achieving an R0 surgery is the mainstay of treatment also in Siewert III adenocarcinoma.

Both proximal and distal margins can be involved. Taking into account proximal margins, resection margins greater than 3.8 cm *ex vivo* in the esophagus

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(corresponding to 5 cm of *in situ* esophagus) were associated with improved survival for all Siewert types [13]. Again, considering only types II and III, no positive proximal margins were reported with a 6 cm wide resection [14]. Conversely, Mine et al. found that a proximal margin of more than 20 mm measured on the resected specimen stretched out on a corkboard (approximately 28 mm in vivo) was related to better survival in Siewert II and III [15]. A distal margin of 4–6 cm is considered safe for all Siewert types [14].

In summary, abdominal total gastrectomy with distal esophagectomy is the treatment of choice for Siewert III adenocarcinoma. A transthoracic approach should be reserved for cases where proximal margins of 5 cm cannot be achieved.

### 23.2.2 Indications According to Lymphatic Spread and Lymphadenectomy

The role of lymphadenectomy in gastric cancer has been extensively discussed in previous chapters. Siewert III is staged as a gastric cancer in TNM 8th ed. and for correct staging at least 16 nodes must be removed. An adequate number of collected lymph nodes is important not only for staging and to avoid stage migration, but also for prognosis. Total number of resected nodes is a good indicator of lymphadenectomy adequacy also in the esophageal cancer: many trials reported a 5-year overall survival advantage in the case of increased number of resected nodes [16, 17], even considering only pN0 gastric cancer [2]. This advantage was noted especially in advanced cancers.

The need for correct lymphadenectomy remains also after induction treatments. Although nodes are harder to detect after induction treatments, their number seems uninfluenced by the treatment [18].

The number of nodes is not the only selection criterion for lymph node dissection: the other key element is lymphatic spread: Siewert type III cancers arise on the proximal stomach and invade the distal esophagus, and nodal diffusion is mainly towards the abdomen in both Western and Eastern series. Nodal abdominal stations are always involved in N+ patients, and around 10% of them have simultaneous positive mediastinal nodes (station 110 according to the IGCA classification) [19–22]. The risk of mediastinal nodal involvement increases with the length of esophageal invasion, also after induction treatments, with a cut-off of esophageal invasion ≥2 cm [23, 24].

Paracardial (stations 1 and 2), lesser curvature (station 3) and left gastric artery nodes (station 7) are the most frequent abdominal stations involved, followed by celiac trunk, common hepatic artery, splenic artery and infrapyloric nodes (stations 9, 8a, 11 and 6). Para-aortic nodes around the left renal vein (station 16A2lat) are positive in around 22–30% of locally advanced cases [19, 25, 26]. Some authors reported a survival benefit from dissection of para-aortic nodes similar to that of second-tier nodes like station 9 [25]. Moreover, prophylactic para-aortic lymphadenectomy after induction treatment could also be beneficial in patients with poorly cohesive and signet-ring cell tumors [27].

As in proximal gastric cancer, no survival advantage is reported when adding splenectomy to D2 lymphadenectomy [25, 26], and splenectomy should only be added to obtain an R0 resection [9].

In summary, because of the risk of nodal involvement and nodal diffusion, all patients ≥T1sm should undergo a D2 abdominal and inferior mediastinal lymphadenectomy. A D3 lymphadenectomy should be considered in advanced poorly cohesive cancers after induction chemotherapy.

## 23.3 Multimodal Treatment

Surgery with lymphadenectomy is the standard approach to Siewert III ≥ cT1sm. R status and nodal involvement are the main prognostic factors [8, 9]. Surgery alone is possible for cT1smN0 patients. However, the high risk of non-curative resections and low survival with surgery alone in locally advanced and N+ cases encouraged the development of multimodal treatments, which reported a survival advantage and increased rate of curative resections after multimodal approaches compared to surgery alone [5, 6]. Multimodal treatments may increase R0 rate and reduce nodal involvement. Induction or perioperative chemotherapy is indicated in all ≥cT3 patients irrespective of clinical nodal status (cN), due to the very high risk of nodal involvement and non-curative resections.

Also all cN+ patients should be offered multimodal treatment [6, 10]. Debate is still open for cT2N0. Risk of nodal involvement of cT2 patients is considerable, reaching 55% as reported by Stiles et al. [11], thus many clinicians and guidelines offer multimodal treatments also to cT2N0 patients [6, 10].

Among multimodal treatments, perioperative chemotherapy is more frequently used. Nonetheless, postoperative cycles are completed only in around half of the cases with any chemotherapy regimen [12]. Among gastric cancers, Siewert III undergo more complicated procedures and the risk of non-completion of postoperative chemotherapy is higher, hence probably induction chemotherapy, without postoperative cycles, would better fit Siewert III patients, but the literature on the topic is scanty [6, 10].

## 23.4 Hot Topics

Tumors at the level of the EGJ are a “zone disease” rather than an “organ disease” [28]: that is the reason why it is difficult to consider all the three Siewert types as a single disease, sharing the same biology, but showing a different behavior only due to their position. Likewise, Siewert III does not seem to be just a slightly higher proximal gastric cancer. As stated several times in this volume, the real revolution in the understanding of gastric cancer started with its molecular classification; nevertheless, most of EGJ cancers were classified as chromosomal instability (CIN). Only Siewert III tumors exhibited features attributable to the other three molecular types, although in different percentages with respect to the other gastric sites [29].

Recently, transcriptomic profiling revealed a different gene expression when comparing Siewert I and Siewert III or Siewert II and Siewert III tumors [30]. For this reason, in the near future we do not only need to borrow the rules of esophageal and gastric cancer as regards resection margins and lymphadenectomy: we will need to evaluate tumors not by site but by molecular pattern. A practical and current example is represented by Siewert III genomically stable/poorly cohesive cancer: considering its highly aggressive submucosal and lymphatic spread, esogastrectomy should be considered to achieve a truly R0 resection. A further evolution of the concept could be to perform esogastrectomy also in Siewert II and proximal gastric genomically stable/poorly cohesive cancers.

The last hot topic is related to a technical aspect: Siewert III cancer surgery requires, as mentioned above, a proximal resection margin of at least 5 cm in the distal esophagus. This implies that the anastomosis would fall very high into the posterior mediastinum, and performing this reconstruction via a minimally invasive approach is demanding and few data are provided the in literature.

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# Gastric Cancer: Synopsis of Treatment Indications

# 24

Giovanni de Manzoni and Franco Roviello

## 24.1 Introduction

After a detailed discussion in the previous chapters about the diagnosis, staging and treatment of gastric cancer, this chapter aims to offer a summary of the therapeutic indications in order to facilitate the clinical application of the most innovative treatment concepts.

We have distinguished these indications according to three different pathways for early gastric cancer (EGC), advanced gastric cancer (AGC), and stage IV gastric cancer (stage IV GC), represented in dedicated algorithms. For each category, alongside the therapeutic algorithm, the points of greatest debate are explained in specific clinical questions.

## 24.2 Early Gastric Cancer Treatment Indications and Clinical Questions

The therapeutic pathway for EGC is synthetized in Fig. 24.1 and references to specific clinical questions (CQ) are flagged in the related steps.

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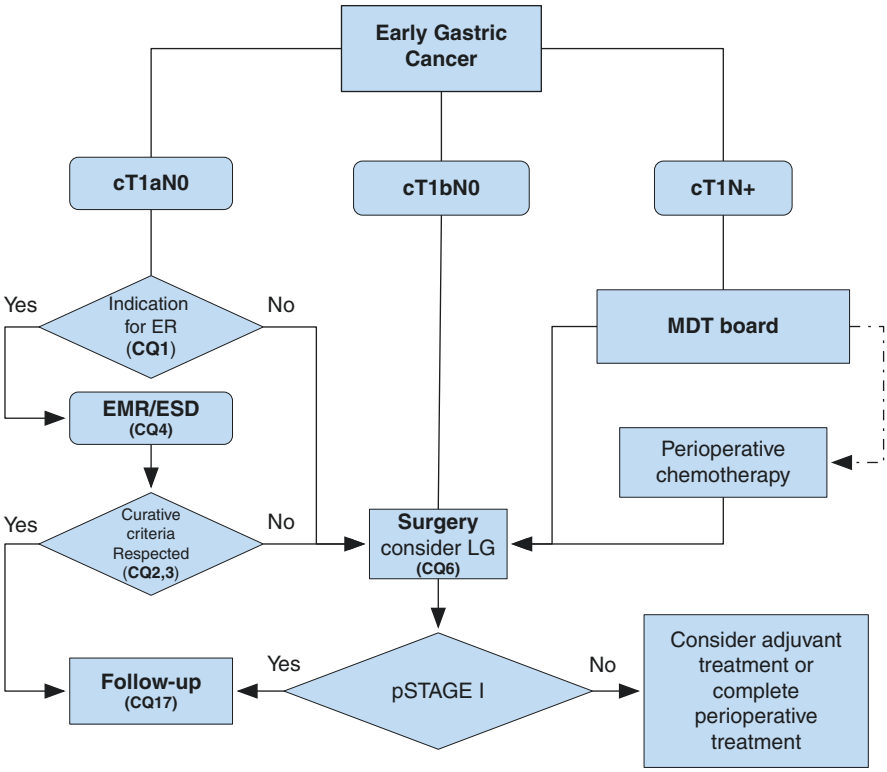


**Fig. 24.1** Early gastric cancer therapeutic path. *CQ* clinical question, *ER* endoscopic resection, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *LG* laparoscopic gastrectomy, *MDT* multidisciplinary team

- *CQ1—What are the indications for endoscopic resection?*
  The indications to perform an endoscopic resection are based on two main concepts: the ability to perform an en-bloc resection and the probability of not having metastatic lymph nodes. Therefore, endoscopic resections should be proposed in patients with well-differentiated intestinal-type gastric adenocarcinomas, limited to the mucosa without ulcerative findings [1, 2].
- *CQ2—When is an endoscopic resection considered curative?*
  An endoscopic resection is considered curative when all of the following criteria are met: pT1a, intestinal histotype, en-bloc resection, negative resection margin, no lymph-vascular infiltration, absence of ulcerative findings and tumor dimension $\leq$2 cm. In this category, the risk of lymph node metastases is virtually absent [2].
- *CQ3—Can the new absolute criteria for endoscopic submucosal dissection (ESD) be accepted in Western countries?*
  In the more recent version of the Japanese guidelines, the absolute criteria for ESD have been extended. In detail, in cases of well-differentiated, intestinal-type gastric adenocarcinomas, limited to the mucosa:

  - dimension is no longer a discriminating factor for ESD in the absence of ulcerative findings;
  - cases with ulcerative findings, lesions up 3 cm are candidates for ESD [2]. Of note, if these criteria are identified in the pathological specimen after ESD, no additional treatments are indicated [2].

    From the oncological point of view, these new absolute criteria for ESD are acceptable; however, in in the West this could raise some feasibility issues, so these cases have to be evaluated in centers with an endoscopist with high ESD experience and should be centralized.

- *CQ4—Which type of endoscopic resection is recommended?*
  ESD is recommended as the treatment of choice for most gastric superficial neoplastic lesions; endoscopic mucosal resection (EMR) is an acceptable option for lesions smaller than 10–15 mm. En-bloc resection rates as well as R0 resection rates are higher for ESD than for EMR, also in lesions smaller than 10 mm; this inevitably affects local recurrence, which is significantly higher after EMR [3]. Conversely, ESD carries an increased risk of perforation, even though in most cases perforations during ESD are managed endoscopically with a conservative approach [4].
- *CQ5—What is the optimal nodal dissection in patients with EGC?*
  D2 lymphadenectomy has shown clear survival advantages in AGC over less extended lymphadenectomies and is therefore globally recognized as a gold standard for such patients.

  In contrast, the nodal dissection of EGC is not yet clearly defined. In the latest Japanese guidelines, in patients with cT1N0 tumors D1 and D1+ lymphadenectomies are recommended [2]. Unfortunately, particularly in the West, some forms of EGC (Laurén's diffuse tumors and Kodama's PenA tumors) showed a particular lymphotropism; of note, such characteristics are not always available on diagnostic biopsies [5, 6]. Therefore, in some subgroups of EGC patients a less extended lymphadenectomy could be an inadequate treatment and, in consideration of the non-negligible incidence of lymph node metastases and skip metastases, a D2 lymphadenectomy should be preferred.
- *CQ6—What role for laparoscopic gastrectomy in EGC?*
  Laparoscopic distal gastrectomy for EGC has been shown to be comparable to open distal gastrectomy in two Eastern randomized clinical trials, both in short- and long-term outcomes [7, 8].

  The Eastern experience can be transposed to the Western reality in high-volume centers with experienced surgeons. However, in the West a D2 lymphadenectomy, in particular in patients with more aggressive forms of EGC, should be taken into account.

  Laparoscopic total gastrectomy is a technically challenging procedure and some concerns are still present particularly for the esophagojejunal anastomosis technique, which is still not standardized. From a propensity score matched analysis of a large Japanese retrospective series, the incidence of anastomotic leakage, readmission and reoperation rates were higher in the laparoscopic group [9]. Therefore, the results of more randomized controlled trials (RCTs) are awaited to draw clearer conclusions on this topic.

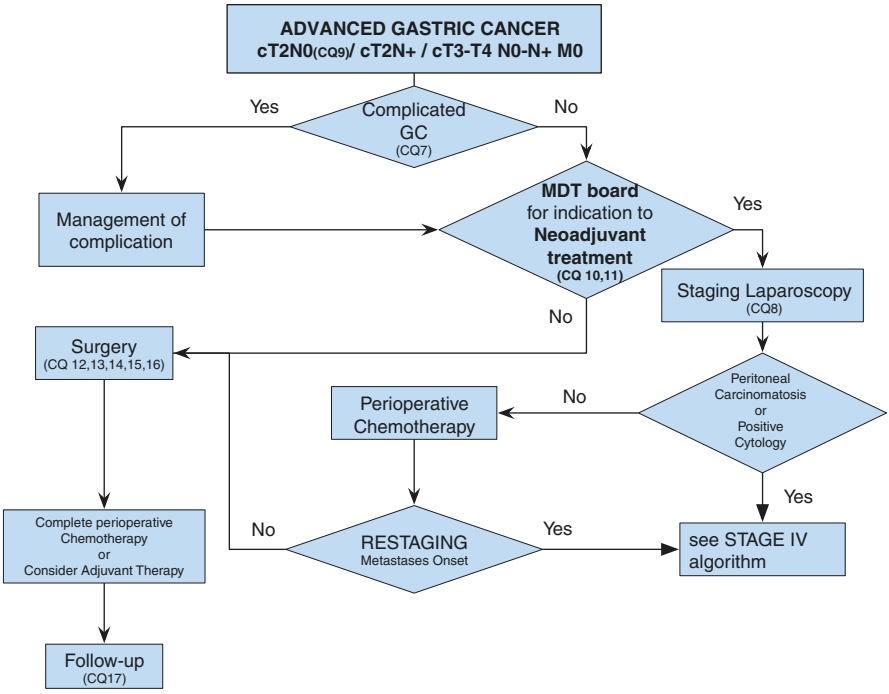


**Fig. 24.2** Advanced gastric cancer therapeutic pathway. *CQ* clinical question, *MDT* multidisciplinary team

## 24.3 Advanced Gastric Cancer Treatment Indications and Clinical Questions

The therapeutic pathway for AGC is synthetized in Fig. 24.2 and references to specific clinical questions (CQ) are flagged in the related steps.

- *CQ7—How to manage complicated gastric cancer?*
  Gastric cancer patients may present with serious complications: gastric outlet obstruction (GOO), overt bleeding (OB) and perforation.

  In the case of GOO and OB, if clinically N0, radical gastrectomy is the best choice; endoscopic or angiographic procedures could be considered as a bridge to surgery in OB cases. Otherwise, in cases of clinically detectable nodal metastases (cN+), neoadjuvant treatment is indicated; in such cases the clinician should make efforts to manage the complication conservatively in order to guarantee the optimal therapeutic approach to the patient.

  In the case of perforation, an emergency surgical approach is almost always necessary. The choice to perform a one- or two-stage radical gastrectomy is dictated by the patient's clinical condition, and specifically by the hemodynamic stability.

- *CQ8—What are the indications to perform staging laparoscopy?*
  Patients with potentially resectable AGC should undergo staging laparoscopy before a neoadjuvant treatment, in order to detect occult peritoneal metastases and positive cytology. Factors associated with a higher probability of peritoneal metastases are clinical T3/T4 tumors, diffuse histotype (poorly cohesive according to the WHO), linitis plastica and suspicious computed tomography findings; with the presence of two or more of these factors, staging laparoscopy should be performed before starting the therapeutic pathway [10, 11].
- *CQ9—cT2N0 upfront surgery or perioperative chemotherapy?*
  Patients with cT2N0 gastric cancer should be always evaluated by a multidisciplinary team in order to choose the proper treatment, where the most important determinant is the accuracy of clinical staging. Theoretically in such cases upfront surgery should be the best treatment option. The main risk is clinical under-staging, which is not uncommon in this setting. If this happens, adjuvant treatment is warranted. As a result, the therapeutic choice in patients with clinically cT2 tumors remains highly controversial and not obvious.
- *CQ10—Why should neoadjuvant or perioperative chemotherapy be considered? What drugs to use?*
  The aims of these treatments, in stage II–III patients, are systemic control of the disease through the treatment of micrometastases, downstaging of the lesions with an increase of the R0 resection rate after and thus an improvement of long-term outcome.

  The strongest evidence currently available is for the FLOT schedule [12]; in selected cases it may be reasonable to use fluoropyrimidine-platinum doublet or triplet [13].
- *CQ11—Does the indication for perioperative chemotherapy change according to age?*
  Currently there are no dedicated studies to answer this question. Subgroup analyses in both the MAGIC [10] and FLOT4 [12] trials did not show any significant differences in different age groups (70 as a cutoff). However, the elderly patients enrolled in the above-mentioned studies had adequate organ function in the absence of important comorbidities. Consequently, some concerns still exist with regard to multimodal treatment in elderly and comorbid patients, who should be evaluated by the multidisciplinary team. In patients older than 70 years, who are candidates for perioperative chemotherapy, closer monitoring of toxicities should be recommended during the perioperative treatment [14].
- *CQ12—When to consider extending lymphadenectomy beyond D2?*
  The role of therapeutic para-aortic lymphadenectomy, i.e., the dissection of station 16a2b1 lymph nodes in the case of clinically detected metastases at this site that respond to preoperative chemotherapy is increasingly gaining ground on the basis of Japanese trials [15]. In this context, dissection of other "posterior" stations (8p, 12p, 13) could have similar indications even though no specific data are available so far.

  The role of prophylactic para-aortic node dissection in the era of multimodal treatment has been hypothesized for some subgroups of patients such as those

with extensive/bulky nodes in the D2 area; however, some other cases, based on histological or molecular subtypes, could benefit from lymphadenectomies more extended than the standard D2 [16, 17]. Also in the prophylactic setting, the benefit of dissecting other posterior stations should be evaluated.

An ongoing RCT of the Italian Research Group for Gastric Cancer (GIRCG) on this topic will provide a definitive answer to these questions (ClinicalTrials.gov Identifier: NCT03961373).

- *CQ13—Omentectomy for AGC*
  Currently, there are no data from randomized studies about omentectomy. The survival advantage in patients who have a complete over a partial omentectomy is not known. However, in accordance with the most recent guidelines [1, 2] omentectomy in cT3 or deeper tumors should be performed, as the risk of omental lymph node metastases or omental tumor deposit could be non-negligible (2% and 8%, respectively) [18].
- *CQ14—Splenectomy for AGC*
  Splenectomy is a procedure associated with an increased risk of morbidity, specifically operative blood loss and pancreatic fistula, without a clear prognostic advantage in most cases [19]. At present, splenectomy is no longer mandatory for station 10 clearance [2] but it is still recommended for:

  1. bulky nodes in station 10;
  2. R0 resection in T4b tumor involving spleen and/or pancreas;
  3. cT4a tumors along the greater curvature or the posterior wall of the upper half of the stomach.

- *CQ15—Bursectomy for AGC*
  Bursectomy is no longer recommended in most recent Japanese guidelines, during standard D2 gastrectomy also in serosal tumors located in the posterior wall [2, 20]. In experienced hands, bursectomy is a low-risk procedure, and it could be important in the multimodal management of patients with peritoneal metastases with a low peritoneal cancer index (PCI) $\leq$6, in order to obtain CC0 in the setting of conversion surgery.
- *CQ16—What role for laparoscopic gastrectomy in AGC?*
  From the evidence currently available, minimally invasive surgery for distal gastric tumors could be considered a feasible procedure when done by experienced surgeons, although it does not yet represent the standard of treatment. Two Eastern RCTs [21–24] have evaluated the oncological and surgical safety of laparoscopic distal gastrectomy and judge this procedure as feasible. Unfortunately, these trials have some limitations due the non-enrollment of patients who underwent neoadjuvant therapy and the exclusion of those with extensive/bulky node involvement at diagnosis; in the latter category of patients, lymph node retrieval during laparoscopic gastrectomy could be inadequate, as shown by COACT1001 [25].

  As stated above, laparoscopic total gastrectomy (LTG) remains a technically demanding procedure with unsolved safety issues, particularly regarding the

esophagojejunal anastomosis. Recently, the STOMACH trial [26], the only available Western RCT, showed similar outcomes in postoperative complications and comparable D2 compliance between open versus minimally invasive total gastrectomy after neoadjuvant chemotherapy; however, solid data on long-term survival are still missing. The results of LOGICA-trial (ClinicalTrials.gov Identifier: NCT02248519), another Western RCT on the role of laparoscopic gastrectomy in AGC, will be soon available. Therefore, LTG in patients with AGC should still be considered under investigation.

- *CQ17—Should follow-up after gastrectomy for cancer be offered to patients?*
  Regular clinical and radiological follow-up should be recommended according to the main consensus currently available, the Charter Scaligero on gastric cancer [27].

  Although there is no clear evidence of a better survival for early diagnosis of gastric cancer recurrence in asymptomatic patients, theoretically this may allow for treatment that may otherwise be more challenging in symptomatic patients. This, in the era of molecular treatment, would likely have a benefit also in progression-free survival.

  In addition to an oncological reason, regular follow-up can lead to benefits in terms of management of post-gastrectomy symptoms, psychological support and scientific research.

## 24.4 Stage IV Gastric Cancer Treatment Indications and Clinical Questions

The therapeutic pathway for stage IV GC is synthetized in Fig. 24.3 and references to specific clinical questions (CQ) are flagged in the related steps.

- *CQ18—What does oligometastatic disease mean?*
  There is no univocal and clear definition of oligometastatic disease in the literature [28–31]. Oligometastatic disease is represented by limited metastatic spread that could take advantage from aggressive multimodal treatment [32]. In our opinion, this should not be a static definition but a dynamic one that integrates a good response to chemotherapy and the possibility of achieving an R0 surgical resection. Thus, oligometastatic disease is characterized by a single site and limited metastatic spread at diagnosis such as PAN+, <3 liver M+, Cyt+, Krukenberg tumor and peritoneal carcinomatosis with a PCI $\leq 6$ that shows clinical response to intensive chemotherapy.
- *CQ19—Is the type of chemotherapy different between oligometastatic and highly metastatic disease?*
  Oligometastatic and highly metastatic gastric cancer patients, although both belonging to stage IV, have different treatment perspectives and prognoses. In fact, while in the first case intensive chemotherapy and surgical integrated treatment is conceivable, in the second one surgery is feasible only in extraordinary cases. Therefore, the purposes and methods of treatment in these two categories are different. In the case of oligometastatic patients, a more active and intensive chemotherapy, such as a triplet regimen (i.e., FLOT), can be hypothesized in

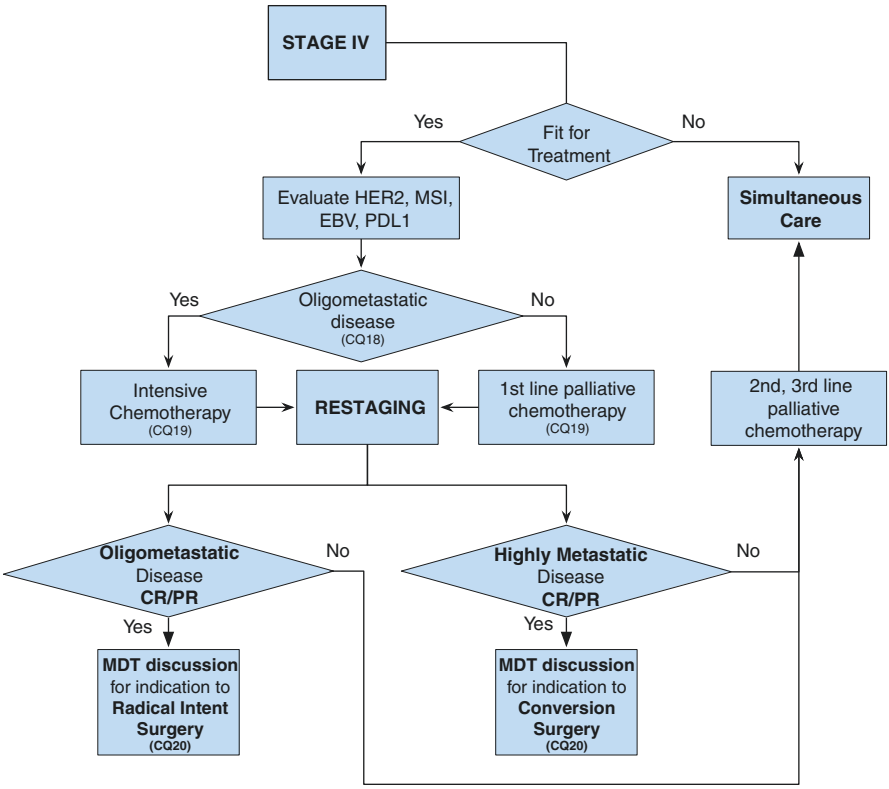


**Fig. 24.3** Stage IV gastric cancer therapeutic pathway. *CQ* clinical question, *CR* complete response, *PR* partial response, *MDT* multidisciplinary team

order to achieve a tumor response that allows radical intent surgery. In highly metastatic patients, a regimen with a more favorable toxicity profile should be used, in order to preserve quality of life and progression-free survival as much as possible.

The introduction of target therapy and immunotherapy can expand the indications for surgery in both oligometastatic and highly metastatic stage IV GC patients; the common view is that the patients most likely to benefit from these new treatments are those stage IV GC surgical candidates who are expected to have the best outcomes in terms of survival and R0 radicality.

- *CQ20—Possible surgical indications in stage IV GC*

  Conversion surgery is the surgical treatment aiming at an R0 resection after chemotherapy, in stage IV GC, that were originally technically or oncologically unresectable (i.e., highly metastatic cases) [31]. The concept of the operation can be defined as adjuvant surgery, after exceptional response of the metastatic

lesions, and should be intended as residual tumor surgery, regardless of the initial involvement.

Another scenario is represented by oligometastatic disease in which radical intent surgery has a slight conceptual but substantial difference with respect to conversion surgery. It could be defined as surgery aiming at R0 resection based on initial metastatic involvement (technically or oncologically resectable) in the absence of other non-curative factors after a good response to intensive chemotherapy.

Of note, these indications should be carefully evaluated and discussed in the multidisciplinary team.

- *CQ21—Optimal treatment in patient with peritoneal cytology?*
  Gastric cancer with positive peritoneal cytology without peritoneal nodules has been considered as stage IV GC since the 7th edition of the AJCC cancer staging system [33]. Positive peritoneal cytology should be intended as an initial diffuse peritoneal involvement and consequently, in uncomplicated patients, systemic chemotherapy should be the first line of treatment [34]. At the end of first-line chemotherapy, an exploratory re-staging laparoscopy is strongly recommended as different scenarios can arise. In the worst case, there will be a frank progression, thus second-line chemotherapy should be promptly started. On the other hand, disease stability or, even better, negative cytology could occur; in such cases R0 surgery, combined with a local peritoneal treatment (i.e., hyperthermic intraperitoneal chemotherapy, HIPEC), could be indicated in order to improve progression-free and disease-free survival [35].
- *CQ22—In patients with peritoneal metastatic disease, what are the indications for cytoreductive surgery and HIPEC?*
  The role of cytoreductive surgery (CRS) in patients with peritoneal carcinomatosis is constantly evolving. In addition to the canonical prognostic factors, in this setting one of the most important is represented by completeness of CRS, given that CC0 surgery compared to CC1 surgery was associated with better 1- and 3-year survival. The ability to obtain CC0, CRS is closely related to the extent of peritoneal involvement; in fact in patients with a PCI > 7 the probability of obtaining a CC0 cytoreduction compared to patients with PCI ≤ 6 drops from 91 to 42% [36].

  Therefore, the hypothesis of conversion surgery in the context of peritoneal metastases must be taken into consideration in patients with PCI ≤ 6 after a good response to chemotherapy, thus never neglecting tumor biological behavior.

  There is currently no agreement on the usefulness of adding HIPEC to CRS, due to the absence of RCTs. The observational retrospective CYTO-CHIP study [37], the main evidence coming from the Western literature, showed that CRS/HIPEC (median PCI = 6), compared with CRS alone (median PCI = 2) improved overall survival and 5-year recurrence-free survival. Of note, not all the patients underwent neoadjuvant or perioperative treatment (62.8% in the CRS/HIPEC group and 35.1% in CRS group).

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# Part IV

# New Frontiers to Improve Prognosis

# Tailored Treatment Strategies Based on New Molecular Classifications

25

Daniele Marrelli, Karol Polom, and Franco Roviello

## 25.1 Introduction

Gastric cancer (GC), despite the decreasing incidence, is still one of the main causes of death for cancer worldwide. Radical surgery and extended D2 lymphadenectomy is the standard treatment in most therapeutic guidelines, although a more extended dissection (D2+) has been proposed to further improve prognosis in selected cases [1–5]. Advanced stages of GC are still associated with poor survival rates despite radical surgery [6, 7]; therefore, new therapeutic options, such as neoadjuvant treatments, have been proposed in order to downstage the tumor and increase the chance of cure [8, 9]. Advanced multimodality treatments, such as hyperthermic intraperitoneal chemotherapy (HIPEC), are also under study in order to prevent peritoneal recurrence of the tumor, which now represents the main cause of tumor relapse after R0 resection [1, 10]. All these procedures are now part of the modern multimodality approach to GC, and tailored treatments could range from minimally invasive procedures (such as endoscopic resections) to very extended and aggressive therapies (combined resections, HIPEC) [1]. To date, tumor stage, histology and patient's characteristics are the main factors considered in the selection process for different therapeutic options. Recently, novel molecular classifications of GC have been introduced, and extensive research is now ongoing to explore potential clinical applications of biological factors [11, 12].

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## 25.2 New Molecular Classifications of Gastric Cancer

In the last few years, two independent molecular classifications by The Cancer Genome Atlas (TCGA) and Asian Cancer Research Group (ACRG) have been proposed. Both of these classifications showed a simple division of GC into four subgroups, opening new possibilities to treat the disease in a tailored way. The TCGA classification identified Epstein-Barr virus (EBV), microsatellite instability (MSI), chromosomal instability (CIN) and genomically stable (GS) groups [11]. The ACRG divided the GC into MSI and microsatellite stable (MSS) types; then secondarily the MSS was divided into epithelial-mesenchymal transition (EMT), TP53+ and TP53− groups [12] (Fig. 25.1).

The MSI represents the group with elevated mutation rates, with Gastric-CIMP, MLH1 silencing, and mitotic pathways. The EBV group represents a group with a high rate of PIK3CA mutation and PD_L1/2 overexpression, which is especially important in the light of new immunologic therapies. Additionally, in this group, we have EBV-CIMP, CDKN2A silencing, and immune cell signaling. The group represented by CIN has mostly intestinal histology, TP53 mutation and RTK-RAS activation. Finally, GS tumors tend to exhibit diffuse histology as well as CDH1, RHOA mutation, CLDN18-ARHGAP fusion and elevated expression of cell adhesion pathways.

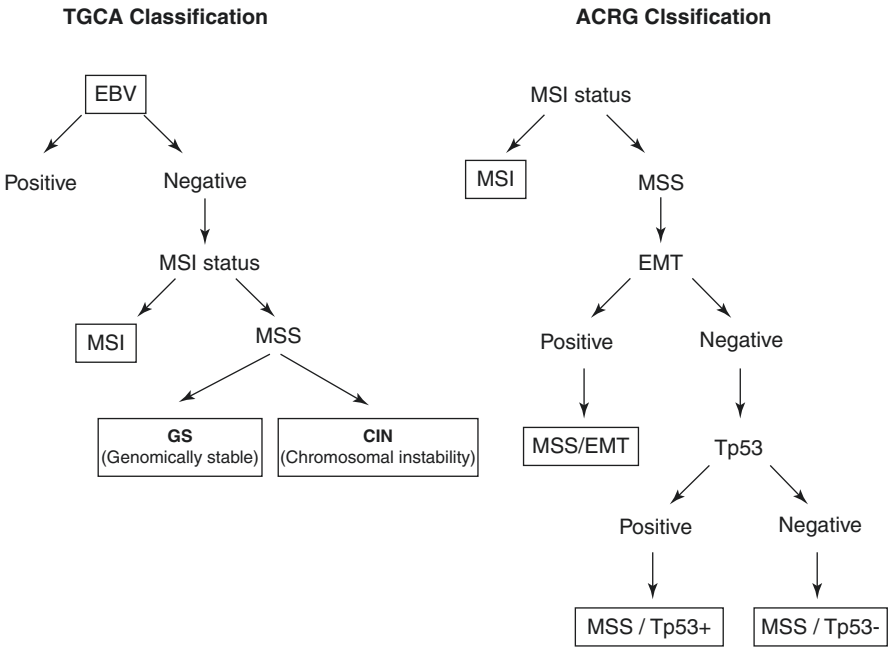


**Fig. 25.1** TGCA and ACRG molecular classifications of gastric cancer. Details are given in the text

The ACRG subtypes also are characterized by specific molecular features [12]. The MSI subtype represents hypermutations of such genes as KRAS, PI3K-PTEN-mTOR pathway, ALK, and ARID1A. The ACRG also found that a subtype of PIK3CA mutation is common in MSI and the other subtypes of that mutation, namely E542K and E545K, are common in MSS tumors. The EMT subtype presents a very small number of mutations. The MSS/TP53− presents a widespread TP53 mutation, and MSS/TP53+ shows a high rate of APC, ARID1A, KRAS, PIK3CA and SMAD4 mutations.

## 25.3 Clinical Impact of Molecular Classifications of Gastric Cancer

Following the introduction of molecular classifications, great research efforts have been conducted in order to clarify their potential impact in clinical decision-making and treatment of GC [13–15]. This is particularly true for the ACRG classification, because in that study some clinically relevant features were attributed to molecular subgroups [12]. Distinct groups, indeed, showed peculiar clinical-pathological characteristics (such as age, tumor location, invasion and stage). Importantly, different prognosis was attributed to the four groups, with MSI showing the best survival rate, and EMT the worst prognosis. The following are the most important molecular subgroups according to these classifications, and their main clinical characteristics identified or suggested to date.

## 25.4 MSI Group (TGCA and ACRG Classifications)

The MSI subgroup is present in both the TGCA and ACRG classifications, and was previously extensively investigated, although with heterogeneous and somewhat conflicting results, mainly due to different characteristics of patient populations and the various tests used for the assessment of MSI status. A recent meta-analysis on 18,612 patients showed that the MSI group accounts for about 9% of the total cases (although in some series it exceeds 20%) [16]. An increased incidence of MSI forms was observed in women, aged patients, intestinal type and distal location. Importantly, the risk of nodal metastases was lower than for MSS cases (odds ratio, 0.70), tumor stage was less advanced, and overall survival was better for patients with MSI gastric cancer (hazard ratio, 0.69). These results confirmed previous investigations by our group. In a recent paper, cancer-related 5-year survival was significantly higher in the MSI-H versus MSS group (67.6 % vs. 35 %), but a stratified analysis revealed a significant impact of MSI on prognosis in non-cardia tumors of the intestinal type or tubular/poorly differentiated histology [17]. We also observed a linear correlation between advanced age and the rate of MSI, and the prognostic effect of MSI status was more evident in elderly compared to younger patients [18]. These findings confirm that MSI may act as a significant predictor of better prognosis above all in the elderly.

In a recent study, a detailed analysis of lymph nodal spread in MSI vs. MSS GC was performed in a total of 361 patients [19]. All patients were subjected to extended (D2) or super-extended (D2+) lymphadenectomy, and the different lymph node stations were divided and classified according to the Japanese Gastric Cancer Association criteria. The MSI tumors showed: a lower rate of lymph node metastases (46% vs. 70% in the MSS group), a lower median number of involved nodes (1 vs. 5), a lower number of involved node stations, and a lower propensity to spread to second- and third-compartment nodes. Furthermore, no skip metastases were observed in the MSI group. These data, once validated in other experiences and in preoperative endoscopic biopsies, could be useful in tailoring lymphadenectomy for GC, allowing a less extended dissection in MSI tumors, above all when faced with high-risk patients with relevant comorbidities [19].

Importantly, MSI status is also related to the response to chemotherapy. In the CLASSIC trial, capecitabine and oxaliplatin adjuvant treatment demonstrated a clear benefit of adjuvant chemotherapy, but no survival benefit was observed in the MSI group [20].

An interesting paper reported a post-hoc analysis of patients included in the MAGIC trial; patients were treated with surgery alone or perioperative chemotherapy plus surgery for operable gastroesophageal cancer, and the association between MSI status and long-term survival was investigated [21]. Results revealed that MSI status was associated with a positive prognostic effect in patients treated with surgery alone, whereas in patients treated with neoadjuvant chemotherapy the prognostic effect was negative. If confirmed, these results could change indications for NAC in the subgroup of patients with MSI.

A meta-analysis pooling data from the CLASSIC, MAGIC as well as the ARTIST and ITACA-S trials found and confirmed no benefit of perioperative or postoperative chemotherapy in MSI-H GC patients [22]. We have to point out here that a new age of immunotherapy showed that especially the MSI group of patients may benefit from this type of treatment.

## 25.5 MSS/EMT Group (ACRG Classification)

The group of tumors with MSS and epithelial-to-mesenchymal transition (EMT) according to the ACRG classification is also very interesting from a clinical point of view. EMT is a process where epithelial cells are transformed into cells with mesenchymal phenotypes, characterized by lost cellular polarity and adhesion and enhanced invasive and migratory properties [23]. Epithelial markers, such as E-cadherin, are repressed, and mesenchymal markers, such as vimentin and fibronectin, are up-regulated. These alterations, together with microenvironment remodeling, facilitate GC aggressiveness, invasion, migration, metastasis and chemoresistance.

Some reports suggest that the EMT phenotype correlates not only with the diffuse type and poorly differentiated histology but also with an advanced TNM stage and poor prognosis [23, 24]. Most information regarding the clinical characteristics of this subtype of GC comes from the ACRG report [12]. It accounts for about 15% of cases, and is associated with younger age (median, 53 years), location in the middle third (45.6%) or the whole stomach (6.5%), diffuse histotype (80.4%) and signet ring cell histology (43.5%); more than 50% of signet ring cell cases belong to the MSS/EMT group. In addition, this subgroup is associated with more advanced pT stage, lymph node metastasis, TNM stage and perineural invasion. Importantly, this group of GC showed the worst prognosis when compared with other groups, and when analyzing the pattern of relapse 77% of MSS/EMT cases in the ACRG cohort recurred in the peritoneum (vs. less than 20% in the other groups); none of the cases had liver metastases [12].

In a recent paper, two distinct molecular subtypes (mesenchymal phenotype and epithelial phenotype) were identified, by analyzing genomic and proteomic data [25]. In particular, the mesenchymal type showed high genomic integrity, characterized by low mutation rates and microsatellite stability, and was associated with markedly poor survival and resistance to standard chemotherapy.

Several data are indicative of a special propensity of EMT or mesenchymal phenotypes to spread to the peritoneum. If confirmed in further studies, this could lead to indications for prophylactic HIPEC in such patients, to attempt to prevent peritoneal recurrence after radical surgery.

## 25.6 CIN Group (TGCA Classification)

The CIN subtype represents about 50% of total GC cases. About 80% of cases in this group are of the intestinal type, and the main location is the fundus/body or EGJ/cardia [11]. This group is particularly interesting in view of a potential targeted therapy; indeed, CIN tumors present amplification in oncogene pathways such as RTK/RAS/MAPK signaling, including HER2, BRAF, epidermal growth factor (EGFR), MET, FGFR2, and RAS [15, 26]. In the series from the MD Anderson Cancer Center, patients with CIN presented the greatest benefit from receiving adjuvant chemotherapy with a hazard ratio for recurrence of 0.39 [27]. Further studies are necessary to elucidate the clinical implications of this group, with special reference to the multimodality approach.

## 25.7 GS Group (TGCA Classification)

The molecular subtype with GS represents about 20% of cases in the TCGA report. Most of these tumors are of diffuse histotype (about 60% of diffuse-type cases are included in this group), and a peculiar characteristic is the predominance of poorly

cohesive-type tumors in this group. Tumors are equally distributed in the stomach portions. The main somatic genomic alterations involve CDH1, ARID1A and RHOA [26]. CDH1 mutations have been reported, also by our group, to be a significant predictor of poor prognosis after radical surgery for GC [28], and this may have clinical implications that deserve further studies. In the abovementioned study from the MD Anderson Cancer Center, the GS group showed no benefit of adjuvant chemotherapy [27].

## 25.8 EBV-Associated Group (TGCA Classification)

The molecular subtype with EBV represents about 9% of cases according to the TCGA report [21]. The molecular analysis showed that this subtype represents PD-L1/2 overexpression, PIK3CA mutation, EBV-CIMP, CDKN2A silencing and additionally immune cell signaling [11]. In the ACRG classification, EBV is mostly seen in the MSS/TP53+ subgroup [12]. A large pooled analysis on 4599 GC patients showed that this group is associated with male gender, early stages, cardia localization, diffuse histotype, and higher median survival [29]. In multivariate analysis, EBV status was one of the statistically significant predictors of survival. Currently, ongoing trials are trying to find a group of patents that will respond to immunologic therapy. Especially the PD-L1/2 expression seen in this GC subgroup is an important target for this type of therapy. Response to this treatment is not only limited to the presence of the antigen but other factors may also play an important role. One of them seems to be EBV infection probably because of its immune cell signaling. Prospective trials are awaited.

## 25.9 Conclusions

Treatment options for GC have been changing in recent years from a standard to a tailored approach. Different individualized procedures can range from endoscopic resection, D2 with an open or minimally invasive approach, neoadjuvant therapy followed by extended surgery, or the addition of HIPEC. The new molecular classifications of GC are expected to be included in the multidisciplinary treatment of this aggressive disease (Fig. 25.2), in particular when their clinical and therapeutic implications are clarified in the near future in a flourishing scientific context of precision medicine.

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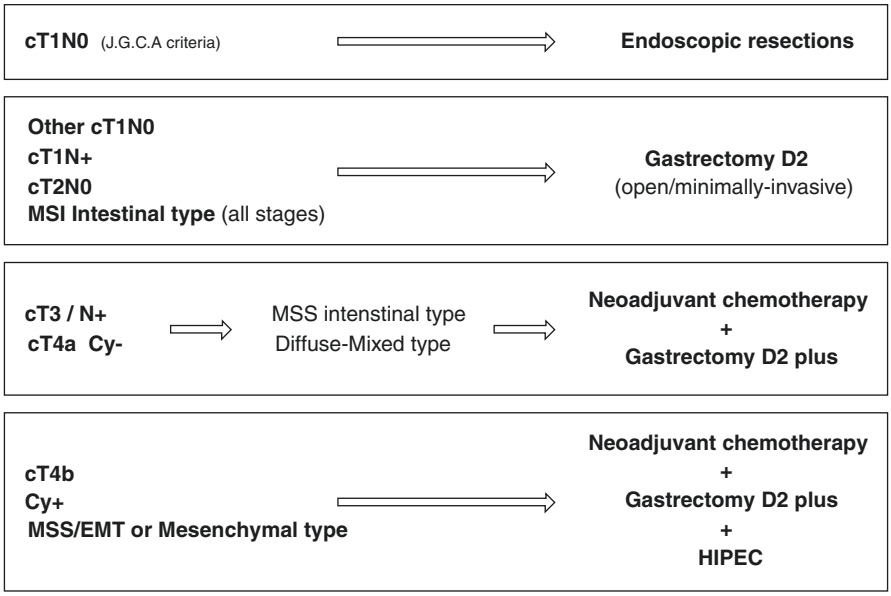


**Fig. 25.2** Proposal of a multimodal approach to non-cardia gastric cancer according to cTNM stage, histotype and molecular features

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# Surgical Navigation in Gastric Cancer

# 26

Luigi Marano and Karol Polom

## 26.1 Fluorescent Navigation

Since 2005, when a first experience of fluorescent sentinel node biopsy in breast cancer patients was published by Kitai et al., we have seen an increasing interest in this novel image-guided possibility that may navigate the surgeon during operation [1]. The most commonly used fluorophore that is visible in near-infrared light is an indocyanine green (ICG) [2]. It is a small 1.2 nm water soluble anionic amphiphilic tricarbocyanine probe [3]. The small size of this particle is responsible for its fast migration via lymphatic channels. By using a special camera with a near-infrared charge-coupled device we can excite this compound with 778 nm light and then it can be detected by the same camera system with an emission of 830 nm.

## 26.2 Vascular Perfusion

One of the most important complications after gastrectomy is anastomotic leakage [4, 5]. One of the factors that is responsible for this complication is disturbed blood supply. In our daily practice we rely on tissue color and vessel pulsation to evaluate good blood supply of tissues that we want to anastomose. Both factors are dependent on operator experience. Fluorescent angiography for visualization of the perfusion may help in lowering the rate of postoperative leakage. Many studies are available for the evaluation of anastomotic perfusion in cases of esophagectomy,

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and a few are also available for gastrectomy. In a group of 30 patients, fluorescent anastomotic perfusion was performed using ICG as a fluorophore after creation of the anastomosis [6]. Different gaps of visualization for gastric, jejunal, and duodenal sides were analyzed.

Mori et al. studied a group of 100 patients and analyzed parameters such as appearance of ICG fluorescence in either side of the anastomosis [7]. The time difference in ICG appearance between these two points was an independent prognostic factor of anastomotic leak.

## 26.3 Lymphography

The best results in surgery are obtained when a standardized type of operation is implemented in the surgical ward. Currently recommended lymphadenectomy varies between D1+ up to D2 lymphadenectomy according to the T stage [8, 9]. ICG is injected around the tumor and after sufficient time (longer than after sentinel node biopsy) we are able to see not only lymphatic vessels but also lymph nodes along the main gastric vessels. Using this technique during the operation a surgeon may visualize lymph nodes stained with fluorophore in near-infrared light and improve lymph node dissection from each stained station. A randomized controlled trial has proved that a significantly higher number of lymph nodes were resected using lymphography and a better quality of optimized lymphadenectomy was achieved [10]. Another idea involving lymphography was presented by Baiocchi et al. where additional lymph nodes were stained outside standard D2 lymphadenectomy [11]. In a small series of patients, they showed that tailored lymphadenectomy might be possible by using this concept of fluorescent lymphography. Kim DW et al, in a pilot study on 28 patients, reported a sensitivity of 98.9% using fluorescent method [12]. In a series of 592 patients who underwent laparoscopic gastrectomy, fluorescent lymphography had a sensitivity of 95.3% in detecting all metastatic lymph node stations and a sensitivity of 81.3% in detecting all metastatic lymph nodes [13]. Importantly, the sensitivity for detecting metastatic lymph nodes was not below 90% no matter the T stage. This new technique seems to be an attractive supplement to current standards. However, we need to point out some limitations of this method. The first limitation is the penetration depth, which might be an important factor especially in Western world obese patients [14]. Additionally, lymph node involvement may limit the possibility of passing through the metastatic lymph nodes to a higher tier of nodes. Another problem is the effect of preoperative chemotherapy as well as chemotherapy with radiotherapy, especially in upper part of the stomach. Furthermore, this new technique requires standardization of the optimal dose and best depth of ICG injection. Some other clinical situations need to be evaluated like linitis plastica as well as fibrosis and disturbed lymphatic flow following preoperative endoscopic submucosal dissection in cases of early gastric cancer.

## 26.4 Tumor Position

The combination of fluorescent lymphography with intraoperative localization of a tumor using ICG was proposed by Liu et al. [15]. Detection of tumor position especially in early-stage disease might be difficult, and this information may help optimize transection lines. Using a site of injection for lymphography we can easily see the tumor's position and evaluate stapler line during resection. A preclinical study by Hyun et al. proposed the use of ICG mixed with liquid rubber to create a fluorescent rubber band [16]. This rubber band placed endoscopically on the porcine stomach facilitated localization of the clips under fluorescent guidance. The authors also stated that the resection margins were sufficient after resection.

## 26.5 Sentinel Node Biopsy

Sentinel node biopsy is a standard procedure in many malignancies, especially in breast cancer and melanoma. In gastric cancer, because of complex lymphatic drainage, sentinel node biopsy is still not a routine procedure. In a systematic review, the detection rate, sensitivity and accuracy of the radioisotope and dye method were similar [17]. In 2004 Nimura et al. used infrared electronic endoscopy for fluorescent ICG sentinel lymph node visualization [18]. Soltesz et al. started using ICG as a fluorophore in sentinel node biopsy in an animal model and Kusano et al. later applied it to gastric cancer patients [19, 20]. An important concern about the standard use of ICG in gastric cancer sentinel node biopsy is that of impossible staining of metastatic lymph nodes. This, together with a complex multidirectional lymphatic drainage, is responsible for up to 11% of skip metastases. We should also keep in mind that the dye may pass to higher tier lymph nodes. For optimal sentinel node mapping we should wait about 20 min after the injection, as an intraoperative injection showed lower sensitivity than a preoperative one [21].

Another field of interest might be a targeted fluorescent antibody that binds a specific cancer antigen such as carcinoembryonic antigen (CEA). A sentinel node biopsy using CEA-targeted fluorescent-guided surgery was proposed by Vuijk et al. [22]. This targeted fluorescent imaging was also used for primary and recurrent tumor localization in colorectal cancer [23] as well as detection of colorectal and pancreatic liver metastases [24]. The results of similar studies in gastric cancer are awaited.

An interesting alternative for ICG is the use of fluorescein as a fluorophore. A group of 20 patients undergoing laparoscopic distal gastrectomy with standard lymphadenectomy received a peritumoral injection of fluorescein [21]. Fluorescent imaging was performed using blue light with a wavelength range of 440–490 nm from a LED curing light. Sentinel nodes were visible in 95% of patients.

Two other fluorophores are also used in daily practice in fluorescent-guided surgery, namely methylene blue and 5-aminolevulinic acid (5-ALA), which will

probably also find a place in the detection of different aspects in gastric cancer surgery [25]. Maruyama et al. and Kishi et al. during laparoscopy for gastric cancer showed that visualization of 5-ALA using its fluorescent properties may improve staging of the disease [26, 27]. During staging laparoscopy, Kishi et al. detected dissemination in 21% of patients without any other clinical symptoms of peritoneal spread, by using 5-ALA fluorescence guidance.

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# Focus on Poorly Cohesive Gastric Cancer

# 27

Maria Bencivenga and Mariagiulia Dal Cero

## 27.1 Why Should We Focus on This Gastric Cancer Subtype?

With the decrease of *Helicobacter pylori* infection and improved food preservation methods, the incidence of intestinal type gastric cancer (GC) has been declining, while that of Laurén diffuse type, or poorly cohesive (PC) type according to the WHO classification, has increased [1]. Of note, this subtype of GC usually affects young females.

The morphological and biological characteristics of PC cancers have implications on diagnosis, staging and treatment pathways needed for such cases.

GC is classically diagnosed by endoscopy. However, PC tumors frequently show an intact mucosal surface due to the submucosal spread of cancer cells, and may consequently be very difficult to identify by white-light imaging endoscopy. This frequently causes diagnostic delays with a dramatic impact on prognosis. Therefore, whenever the symptoms fail to resolve or alarm symptoms appear in the absence of a diagnosis [2], endoscopy should be repeated more than once; if the findings remain negative, imaging techniques such as endoscopic ultrasound with deep biopsies or computed tomography scan should also be performed. PC tumors are also more difficult to characterize in terms of morphological and molecular aspects in gastric biopsy specimens, and for this reason more than the standard 5–8 biopsies would be required during diagnostic endoscopy when a PC is suspected based on tumor macroscopic appearance.

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Staging of PC cases is mainly based on computed tomography scan, on which thickened stomach wall, high-degree contrast enhancement, and higher frequency of diffuse infiltrative gross appearance are typical findings, particularly if these features are combined [3]; positron-emission tomography is less useful because of lower SUVmax and 18F-FDG avidity of PC cancers, with frequent false-negative cases [4]. Another important staging tool especially in PC tumors is exploratory laparoscopy, as these cases are indeed at high risk for occult peritoneal disease or positive peritoneal cytology and laparoscopy could avoid understaging [5].

With regards to biological behavior, PC GC shows some peculiarities: at early stages, when limited to the gastric mucosa or submucosa, they have a better prognosis compared with all the other GC subtypes, but when they progress through the gastric wall, they become extremely aggressive in most cases [6, 7]. Indeed, locally advanced PC GC have a high risk of positive resection margins due to unsuspected submucosal tumor spread and they carry a high rate of nodal metastases requiring extensive lymphadenectomies compared to non-PC types. Furthermore, the worst scenario occurs when these tumors arise in the gastric serosa: in such cases, even after a radical gastrectomy, the risk of peritoneal recurrence is high, but unfortunately also very often, already at time of staging laparoscopy, a positive peritoneal cytology or even peritoneal metastases are found limiting the chance of curative-intent surgery and long-term survival. Moreover, most but not all locally advanced PC tumors are reported to be chemoresistant with evidence of cancer progression during preoperative chemotherapy [8]. As such, these cases should be treated differently from the current standard of a perioperative multimodal scheme.

Nevertheless, a subgroup of advanced PC cases still behaves less aggressively and could also be chemosensitive, thus benefiting from standard treatments.

The long-term prognosis of advanced PC tumors is controversial. The reported discrepancies on prognosis may reflect different pathogenetic mechanisms, but may also be due, at least partly, to the lack of standardization in the pathological definitions and classifications used, which causes the improper comparison between subgroups of tumors with different biological characteristics. Indeed, the WHO category of PC tumors includes the signet ring cell (SRC) type that are PC cases in which most of the tumor cells display the peculiar morphology of a central, optically clear, globoid droplet of cytoplasmic mucin with an eccentrically placed nucleus. However, frequently the terms PC and SRC are used indiscriminately. Moreover, often the Laurén category of diffuse type, the Japanese category of poorly differentiated type or even the macroscopic type of *linitis plastica* are mixed up with the WHO categories of PC and SRC.

Based on these epidemiologic and clinical considerations, PC tumors need special attention. Unfortunately, so far due to the low incidence of GC in Western countries, efforts to deepen the knowledge of its subtypes have been insufficient, while in Eastern countries, where the incidence of GC is higher, thanks to the adoption of

nation-wide screening programs, most cases are diagnosed at early stages, limiting the dramatic impact of poor prognosis of advanced PC cases. As a consequence, there is an urgent need for Western studies focused on PC tumors. Such studies these should aim to:

- uniform the histopathological definitions to be used to allow the comparison between homogeneous subgroups of gastric cancer;
- define tailored diagnostic and therapeutic algorithms;
- understand the molecular mechanisms of cancer progression of this subtype of GC; a clinically relevant integration of molecular and morphological aspects of PC cancers should then be provided.

## 27.2 The Way to Solve the Issue of Pathological Definitions and Classifications

Three histological classifications are the most used for GC: the Laurén, the Japanese and the WHO classifications. Of note, the Laurén diffuse type corresponds to the PC type of the WHO classification, and this overlaps with the non-solid type poorly differentiated adenocarcinoma category according to the Japanese pathological system. Thus, in order to solve the issue of different classifications, the WHO category of PC tumors should be universally routinely used.

The second problem to solve is how to define, among PC tumors, signet ring cell cancers (SRCC). These are defined as PC cases in which most of the cancer cells have signet ring morphology, but the percentage of SRCs needed to define a carcinoma as a SRCC has never been clearly specified. In order to harmonize the definition of SRCC worldwide, on behalf of the European Chapter of the International Gastric Cancer Association a new classification of PC type cancer based on the amount of SRCs has recently been proposed.

In detail, PC tumors were coded into three categories [9]:

1. "pure" signet ring cell cancers having ≥90% of signet ring cells (SRCC);
2. poorly cohesive carcinoma with signet ring cell component between >10% and <90% (PCC/SRC);
3. PC not otherwise specified carcinoma with ≤10% of signet ring cells (PCC-NOS).

Of note, the present subdivision of PC tumors is reported in the recent WHO classification [10]. Then, by using such a classification, a multicenter European study [11] found that the proportion of SRCs was inversely related to the depth of tumor invasion and nodal status. Moreover, the amount of SRCs was shown to have an independent impact on cancer-related survival, with "pure" SRCC having the best prognosis among the PC categories.

Interestingly, a recent report by Korean authors showed similar results [12].

## 27.3 Current and Future Perspectives of Tailored Treatment for Poorly Cohesive Tumors

In clinical practice there are already tendencies to treat PC differently from other GC subtypes, even if no clear indications are reported in the guidelines. For instance, surgeons tend to provide large resection margins in gastric PC cancers [13], but only German authors suggest 8 cm as an optimal length for proximal resection margins in these cases [14]. Also, more extended lymphadenectomies are chosen by surgeons expert in PC tumors [13]. An interesting hypothesis is that more extended lymphadenectomies, such as D2+/D3 dissections, provide a better local control of disease in tumors with PC histology. Both the surgical topics of extended resection margins and lymphadenectomies according to cancer histology are being addressed by ongoing European trials.

Moreover, some warnings about laparoscopic approaches in locally advanced PC GC were issued as they are related to a higher rate of positive surgical margins compared to intestinal type tumors: Kelly et al. showed a 10% of R1 resections after laparoscopy compared to 1% of the open approach and, among these R1, 75% were PC tumors [15].

The high rate of peritoneal recurrences after radical surgery as well as the non-negligible incidence of synchronous positive peritoneal cytology and of peritoneal carcinosis could require the addition of prophylactic as well as therapeutic intraperitoneal treatments to the current standard treatments.

## 27.4 Topics for Biomolecular Research on Poorly Cohesive Gastric Cancer

The best available evidence on DNA alterations of GC comes from The Cancer Genome Atlas (TCGA) project [16], which classifies GC into four molecular subtypes: microsatellite instable (MSI), Epstein-Barr virus (EBV)-related, chromosomally instable (CIN) and genomically stable (GS). PC tumors mainly belong to the molecular category of GS cancers. In this category, the most frequently mutated genes are CDH1 (37%) and RHOA (15%), involved in cell adhesion; the fusion CLDN18-ARHGAP gene is also frequent (15%) and it is mutually exclusive with RHOA mutations.

RHOA is the founding member of the Rho GTPase family comprising important intracellular signaling molecules that regulate the cell cycle and promote the acquisition of epithelial-mesenchymal transition (EMT) [17].

More recently, another relevant study, by analyzing genomic and proteomic data [18], identified two distinct phenotypes in GC: the mesenchymal phenotype (MP) and the epithelial phenotype (EP). The MP was characterized by the activation of EMT, including the TGF-β pathway and such tumors were clinically extremely aggressive, showing poor survival and chemoresistance. Of note, when previously recognized gastric PC tumors were stratified according to MP, a majority of patients

with MP were PC, but only the most clinically aggressive among PC tumors expressed MP signatures. Alterations of the ROHA gene and their correlation with the acquisition of EMT features should be specifically analyzed in PC GC.

Another topic for research is the evaluation of intratumoral immune infiltration. PC tumors have recently been reported to have less immune infiltrate and also, particularly, a low density of tumor-associated macrophages (TAMs) compared to other GC subtypes [19]. As regards more in detail TAMs, conflicting results have been reported on the impact of their amount on prognosis of GC that could be explained by the heterogeneity of TAM populations within different tumors [20]. Characterization of TAM populations and understanding possible cross-talks between tumor and immune cells in the pathogenesis of PC GC would help in identifying potential therapeutic targets and in developing combination strategies to enhance immune recognition of this minimally inflamed GC subtype.

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# Target Therapy and Immunotherapy in Gastric Cancer

28

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## 28.1 Introduction

Recent advances in the knowledge of pathogenesis and biology of gastric cancer (GC) have paved the way to novel and personalized therapeutic approaches.

The Cancer Genome Atlas (TCGA) classification of GC [1] has identified four molecular subtypes for this disease [2], overcoming the histological classification by Laurén and providing a roadmap for the development of targeted therapies (Fig. 28.1). To date, several trials have tested different targeted agents based on specific genetic alterations, leading to their approval especially in the advanced setting (Table 28.1). Moreover, umbrella and platform trials have shown clinical utility of a personalized approach based on the patient's molecular profile [3].

Nonetheless, avoiding immune destruction has been defined as one of the hallmarks of cancer [4]. Immune checkpoint inhibitors (ICIs) act by removing the brakes prompted by cancer cells in order to activate the immune response against cancer cells. Immunotherapy entered routine clinical practice in several cancer types and, more recently, it has had remarkable results also in upper gastrointestinal neoplasms.

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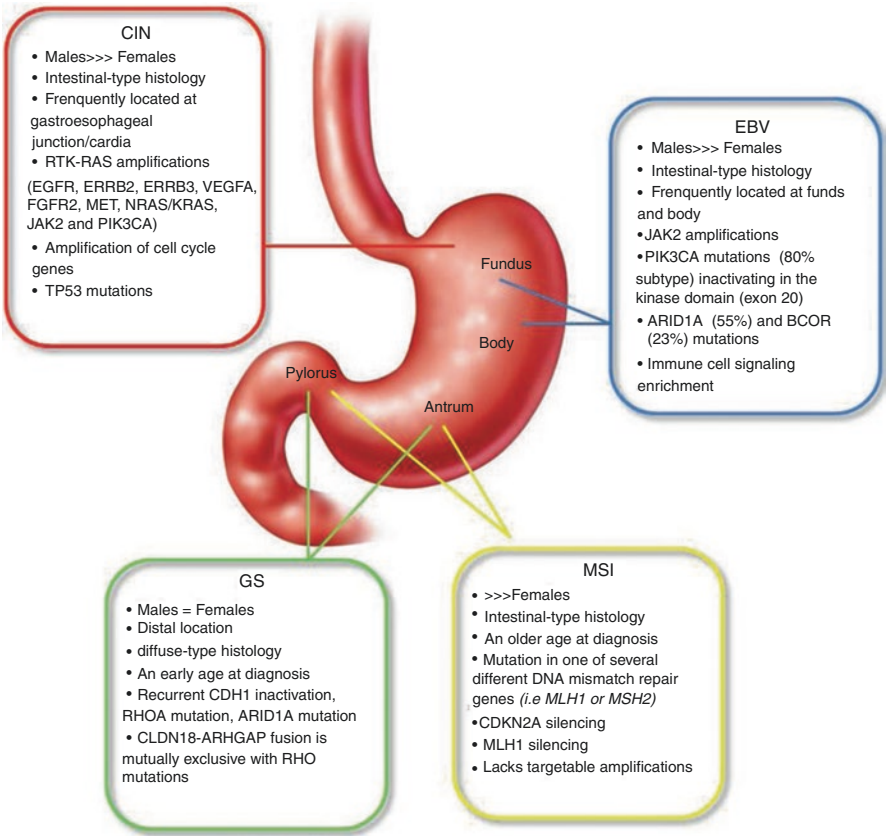


**Fig. 28.1** The most relevant clinical-pathological and molecular features of The Cancer Genome Atlas (TCGA) subtypes. (Reproduced with permission from [2])

## 28.2 Molecularly Targeted Agents

### 28.2.1 Anti-HER2 Agents

HER2 is a tyrosine kinase receptor belonging to the epidermal growth factor receptor (EGFR) family, encoded by the pro-oncogene *ERBB2* located at chromosome 17q2. The amplification of the *ERBB2* gene leads to an overexpression of HER2, which plays a biological and clinically relevant role in different types of cancer, including GC. An estimated 6–23% of GC has overexpression and/or amplification of HER2 [5].

*Trastuzumab* is a monoclonal antibody against HER2, which binds to the extracellular domain IV of the receptor, and the first molecular targeted agent approved for the first-line treatment of advanced GC. In the randomized phase III TOGA clinical trial, patients with HER2-positive advanced gastric or gastroesophageal

**Table 28.1** Relevant clinical trials with molecularly targeted agents in gastric cancer

| Signaling | Molecular target | Therapeutic agents | Clinical trial (identifier) | Phase | Line of treatment |
|---|---|---|---|---|---|
| EGFR | HER2 | 5FU/Capecitabine + Cisplatin ± Trastuzumab | TOGA (NCT01041404) | III | First |
| | HER2 | Perioperative FLOT ± Pertuzumab + Trastuzumab | PETRARCA (NCT02581462) | II/III | First |
| | HER2 | Trastuzumab Deruxtecan vs. Irinotecan/Paclitaxel | DESTINY (NCT03329690) | II | Third |
| VEGF/ VEGFR | VEGFR2 | Ramucirumab ± BSC vs. placebo + BSC | REGARD (NCT00917384) | III | First |
| | VEGFR2 | Ramicirumab ± Paclitaxel | RAINBOW (NCT01170663) | III | Second |
| | VEGFR2 | Apatinib vs. placebo | ANGEL (NCT03042611) | III | Third |
| | VEGFR-1/-2 | Regorafenib vs. placebo | INTEGRATE (ANZCTR 12612000239864) | II | Second/third |
| Claudin 18.2 | | Zolbetuximab | MONO (NCT01197885) | II | Second/third |
| | | Epirubicine + Oxapliplatin + Capecitabine ± Zolbetuximab | FAST (NCT01630083) | II | First |
| FGFR | FGFR2 | mFOLFOX6 ± Bemarituzumab | FIGHT (NCT03694522) | II | First |
| | FGFR3 | Pemigatinib | FIGHTER (Eudra CT 2017-004522-14) | II | Second |

junction (GEJ) adenocarcinoma were allocated to receive trastuzumab in combination with standard fluoropyrimidine plus cisplatin chemotherapy or chemotherapy alone. Combination treatment resulted in an improvement in progression-free survival (PFS) and overall survival (OS) (13.8 vs. 11 months, respectively; P = 0.046), establishing this regimen as the standard treatment for patients with HER2-positive metastatic disease [6].

*Pertuzumab* is a monoclonal antibody binding to the extracellular domain II of HER2, inhibiting, in turn, HER2-HER3 heterodimerization. Although this agent failed to demonstrate efficacy in combination with trastuzumab as first-line treatment for metastatic GC [7], it has been more recently tested in the setting of perioperative chemotherapy. In the phase II/III PETRARCA trial, the addition of trastuzumab plus pertuzumab to perioperative FLOT (docetaxel, oxaliplatin, leucovorin, 5-fluorouracil) significantly improved pathological complete remission and nodal negativity rates in patients with HER2+ resectable esophagogastric adenocarcinoma [8].

The efficacy of different antibody-drug conjugate agents has been recently tested in GC. *Trastuzumab emtansine* (TDM1) failed to demonstrate efficacy in combination with taxane as second-line treatment in advanced HER2+ GC patients [9]. Conversely, the activity of trastuzumab deruxtecan, a conjugate with a topoisomerase I inhibitor was recently evaluated in a phase II study (DESTINY-Gastric01 trial) in patients with HER2+ advanced GC pretreated with at least two lines of therapy, including trastuzumab. Trastuzumab deruxtecan showed a statistically significant improvement in objective response rate (ORR) and in OS, a primary and secondary endpoint of the trial, respectively [10].

### 28.2.2 Antiangiogenic Agents

The inhibition of angiogenesis by targeting the vascular endothelial growth factor (VEGF) axis has shown a major activity in GC. Whereas the monoclonal antibody against the VEGF ligand bevacizumab failed to show significant activity, ramucirumab, a human IgG1 monoclonal antibody VEGFR-2 antagonist, became standard as second-line treatment in advanced GC. Ramucirumab demonstrated to be effective both as single-agent treatment when compared to placebo in the REGARD study, and as combination treatment with paclitaxel when compared to paclitaxel alone in the RAINBOW study [11, 12].

About the use of small molecule kinase inhibitors, controversial results have been reported with the use of apatinib, a selective inhibitor of VEGFR-2, in previously treated advanced GC patients [13]. In the randomized phase 2 INTEGRATE study, the multikinase inhibitor regorafenib prolonged PFS compared to placebo (2.6 vs. 0.9 months, respectively) [14]. A phase 3 study is therefore ongoing (INTEGRATE II, NCT02773524).

### 28.2.3 Targeting of Claudin 18.2

The tight junction protein claudin 18.2 represents a potential novel target of particular interest in GC, as it is expressed in about 85% of cases. Claudin 18.2 blockade with monoclonal antibodies is being investigated. In the phase 2 MONO trial, zolbetuximab, a claudin 18.2-blocking monoclonal antibody, showed an ORR of 9% in 43 patients with recurrent or refractory advanced GC or lower esophagus cancer and achieved an ORR of 14% in a subgroup of patients with moderate-to-high Claudin 18.2 expression in about 70% of tumor cells [15]. The randomized phase 2 FAST study investigated the combination of zolbetuximab with a triplet chemotherapeutic regimen as first line in advanced or recurrent GC and GEJ cancer patients, demonstrating to prolong PFS (median 7.5 vs. 5.3 months; hazard ratio [HR] 0.44).

### 28.2.4 Inhibition of FGFR

The evidence for FGFR2 amplification in 4–6% of GC patients prompted the investigation of different inhibitors of this receptor [16–18]. The addition of the anti FGFR2b humanized monoclonal antibody bemarituzumab to chemotherapy significantly improved PFS and OS versus chemotherapy alone in the frontline treatment of patients with FGFR2b-overexpressing, locally advanced or metastatic GC and GEJ cancer. An autocrine loop established through the overexpression of FGFR3 and its ligand FGF9 was identified as a mechanism of resistance to trastuzumab in HER2+ GC models and patients [19]. A phase II trial with the FGFR inhibitor pemigatinib as second-line treatment in trastuzumab-resistant GC patients is currently active to demonstrate this hypothesis [20].

## 28.3 Immunotherapeutic Agents

Immunotherapy through the blockade of the programmed death 1 (PD-1) pathway has changed the paradigm of treatment in numerous human cancers. The common expression of programmed death ligand-1 (PD-L1) in the specific molecular subtypes of GC associated with Epstein-Barr virus infection (EBV+) or microsatellite instability (MSI) prompted the investigation of immunotherapeutic agents in different GC clinical settings [21].

The anti-PD-1 antibody pembrolizumab is currently approved as second-line or subsequent therapy for high MSI (MSI-H)/deficient mismatch repair (dMMR) tumors or as third-line or subsequent therapy for gastric adenocarcinoma with PD-L1 expression levels by combined positive score (CPS) of $\geq 1$.

In the metastatic setting, the introduction of immunotherapeutic agents as part of the first-line treatment has obtained to date controversial results [22]. First positive results with anti-PD-1 antibodies were observed in previously treated GC or GEJ

cancer patients irrespective of PD-L1 status in cohort 1 of KEYNOTE-59 and ATTRACTION-2 trials [23, 24]. However, two phase 3 trials failed to demonstrate a superiority of immunotherapy compared to chemotherapy in pretreated GC or GEJ cancer patients [25, 26]. In the first-line setting, the randomized, global, phase 3 KEYNOTE-062 trial compared pembrolizumab alone or combined with chemotherapy to chemotherapy alone in patients with advanced and untreated HER2-negative GEJ and gastric cancer. Pembrolizumab was non-inferior to chemotherapy in patients with CPS ≥ 1. However, neither pembrolizumab alone nor associated with chemotherapy was superior to chemotherapy, except in the subgroup of patients with MSI-H [27]. More recently, the randomized, phase 2/3, Asian ATTRACTION-4 trial failed to demonstrate longer OS with the combination of nivolumab and chemotherapy in patients with advanced, HER2-negative GEJ or gastric cancer, even if longer PFS and higher ORR were observed. In the randomized, phase 3, global CheckMate 649 trial the combination of nivolumab and chemotherapy has shown longer OS (HR 0.71) and PFS (HR 0.68) compared to chemotherapy alone in patients affected by previously untreated, advanced, HER2-negative or unknown HER2 status esophageal, GEJ or gastric adenocarcinoma with a PD-L1 CPS ≥ 5. The benefit obtained by adding nivolumab was consistent across all pre-specified subgroups and was observed also as more frequent and durable responses, leading to consider nivolumab plus chemotherapy as a new potential standard first-line treatment in this patient population.

In the second-line setting pembrolizumab was not superior to paclitaxel in PD-L1 negative or PD-L1 CPS ≥ 1 GC patients in the KEYNOTE-061 trial [25]. Negative results were also observed comparing avelumab with chemotherapy in patients with GEJ and gastric cancer after second-line therapy [26]. Conversely, in the ATTRACTION-02 trial nivolumab prolonged OS compared to placebo in GEJ and gastric cancer patients after ≥2 lines [24].

In order to overcome immune evasion, combinations of ICIs are being explored [28]. Early signs of activity have been shown with the association of anti-PD-1 antibodies and antiangiogenic tyrosine kinase inhibitors such as lenvatinib or regorafenib [29]. Based on the synergistic antitumor activity, the strategy of combining anti-PD-1 with anti-HER2 agents, such as trastuzumab or margetuximab, in HER2-positive GC patients seems promising.

Some putative biomarkers of response to immune checkpoint blockade have been proposed. Four to 24% of gastroesophageal tumors are characterized by MSI [30]. Mismatch repair deficiency has been reported in retrospective analyses as a putative negative predictive factor to chemotherapy response both in the adjuvant and neoadjuvant setting [31, 32]. Conversely, high MSI has been correlated with higher sensitivity to ICIs in all cancer types. However, the lack of prospective data, in particular with the standard FLOT regimen, currently limits a possible application in daily routine decisions. Nevertheless, this subgroup of patients could mostly benefit from immunotherapy in the localized and advanced setting. Therefore, all patients should be tested for MSI. As in other tumors, the PD-L1 CPS score

represents a useful tool to predict response to ICIs and is already in use in clinical trials [33]. EBV-positive GC are characterized by marked immune cell infiltration and often exhibit PD-L1 and PD-L2 overexpression. Like dMMR, with which it is mutually exclusive, EBV is a positive predictive factor for immunotherapy, but it occurs only in a small subgroup of tumors. More recently, tissue tumor mutational burden has been suggested as an additional biomarker of response to anti-PD-1 molecules.

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# Part V

# Perioperative Management and Follow-Up

# Immunonutrition in Gastric Cancer

# 29

Alessia D'Ignazio and Franco Roviello

## 29.1 Nutritional Status

A careful assessment of nutritional status and systematic nutritional risk screening (NRS) should be considered in all patients with gastric cancer to prevent or correct malnutrition [1]. The NRS [2] score is based on body mass index (BMI), weight loss, decreased food intake and stage of tumor disease. The grade of nutritional depletion is classified as mild, moderate or severe. In association with NRS, it is pivotal to consider the value of preoperative serum albumin as a prognostic factor for postoperative outcomes.

Additionally, the Global Leadership Initiative on Malnutrition (GLIM) criteria recognize tumor-induced inflammation as a determining factor in inducing malnutrition [3], thus emphasizing the crucial role of cancer. The GLIM classification identifies *phenotypic criteria*, such as weight loss, reduced BMI and reduced muscle mass, and *etiologic criteria,* such as reduced intake/assimilation of food and inflammation. To define malnutrition, the combination of at least one phenotypic criterion and one etiologic criterion is required (Table 29.1).

A malnutrition state whose progression depends on the type and stage of the tumor, inflammatory state, anorexia, response to oncologic treatment, and presence of active catabolism is considered cachexia [4]. Accurate staging may evaluate anorexia, reduced caloric intake and catabolic drivers such as systemic inflammation, disease progression, response to treatment, muscle mass measurements, current weight and weight 6 months prior, physical and psychological functioning (Table 29.2).

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**Table 29.1** Phenotypic and etiological criteria of malnutrition

| | | |
|---|---|---|
| Phenotypic criteria | Weight loss (%) | >5% in the past 6 months |
| | | *or* |
| | | >10% beyond 6 months |
| | Low BMI (kg/m$^2$) | <20 for <70 years |
| | | *or* |
| | | <22 for ≥70 years |
| | Reduced muscle mass | Mass reduction measured with validated techniques |
| Etiologic criteria | Reduced food intake or assimilation | Any reduction for >2 weeks or any chronic GI condition that adversely affects food assimilation or absorption |
| | Inflammation | Acute disease or related chronic disease |

*BMI* body mass index, *GI* gastrointestinal

**Table 29.2** Staging of cachexia

| Precachexia | Cachexia | Cachexia Resistant |
|---|---|---|
| • Anorexia<br>• Metabolic alterations<br>• Weight loss <5% | • Weight loss >5% in the previous 6 months<br>• BMI <20 and any weight loss >2%<br>• Sarcopenia and any weight loss >2% | • Procatabolic and unresponsive disease state<br>• Reduced performance status<br>• Reduced life expectancy |

## 29.2 Preoperative Nutrition

Surgery with curative intent remains the mainstay treatment for most gastrointestinal cancers, even though many factors influence the clinical and oncologic outcome. Increased catabolism and systematic inflammation are part of the process known as "disease-related malnutrition" [5], which leads to the development of a vicious cycle that results in nutritional depletion [6].

Undoubtedly, less tissue perfusion brings less oxygen and nutrients, potentially modifying the microbiome [7–13]. In addition to the tumor-induced motility dysfunction, its presence increases delay in healing rate, postoperative complications, reduction of immune response [14] and consequent infections. The nutritional support needed to achieve the adequate caloric intake is strictly related to the nutritional status and the accessibility of nutrient intake, being it oral, enteral or parenteral. A caloric intake of 1.2–1.5 times greater than at rest (30–35 kcal/kg/day) is recommended. The main discerning argument on which all therapeutic planning is based concerns the possibility of using the intestinal tract to administer nutrients, given its capability to maintain sufficient digestive and absorption capacity. Secondly, it is also necessary to consider the expected duration of the patient's inability: artificial nutritional support is appropriate after 7 days or, if the total nutritional intake is 60% lower than required, for more than 10 days.

## 29.3 Immunonutrition

An important meta-analysis suggests that oral support with standard nutrition increases the level of IgA, IgG, IgM, CD4, CD3, CD4/CD8 ratio and NK cell count, improving the nutritional and immunologic status of patients with gastric cancer [15]. Immunonutrition with a supplement of fatty acids, arginine and omega-3 could modulate th1/th2 differentiation and production of IFN-γ, which has an important role on promoting host defense against pathogens [16, 17].

The timing for administration has been studied by various authors, differentiating preoperative, postoperative and perioperative periods.

The ESPEN guidelines recommend the introduction of immunonutrition within 7 days before surgery in malnourished patients; positive results have been demonstrated even for normonourished patients with cancer [18, 19].

Immunonutrition is recommended by the guidelines of various international scientific societies (ESPEN, ASPEN/SCCM, SFAR and SFNEP) as well as the Italian ERAS (Enhanced Recovery After Surgery) protocols, and its clinical efficacy has been demonstrated in numerous clinical studies conducted over 20 years of scientific research. Immunonutrition must be implemented 5–7 days before surgery. It should be enriched with a supplement of arginine, an essential amino-acid that stimulates the immune-mediated T-lymphocyte response, promotes anabolism, nitrogen retention and wound healing; with fatty acids of the omega-3 series, such as alpha linoleic acid; with EPA and DHA derivatives, which modulate inflammatory processes and inhibit the immunodepressing action of the omega-3 series acids; nucleotides, building blocks of genetic material and essential substrates for cells, especially for those with high turnover, such as mucosal cells, lymphocytes and macrophages [20–22].

## 29.4 Nutrition After Surgery

Early oral nutrition has proved effective as part of a postoperative rehabilitation protocol in colorectal, major gynecological, urological and vascular surgery (fast-track surgery or ERAS). It is not yet routinely practiced after gastrointestinal surgery due to the risk of anastomosis dehiscence and postoperative ileus. For patients who cannot tolerate enteral nutrition and patients with postoperative complications limiting the consumption and absorption of adequate intake of nutrients (ESPEN grade A guidelines), parenteral nutrition is required.

The priority is therefore to restore gastrointestinal function early on and prevent the development of a metabolic adaptation to surgical damage, by maintaining an adequate nitrogen balance. This approach suggests, for example, the use of epidural anesthesia and analgesia in order to prevent postoperative ileus, obtain adequate pain control and avoid long periods of fasting and immobilization. The success of such an approach has been shown by numerous studies conducted since the early

2000s (mainly in colorectal surgery), based on which clinical recommendations have been published by the ERAS Society.

A standard unrestricted diet is strongly recommended, starting with minimum nutritional amounts and increasing the intake every 3–4 days, based on the patients' tolerance. In the non-enhanced management area for distal gastrectomy it is common to start oral nutrition 48 h after surgery. In cases of total gastrectomy, with esophagojejunal anastomosis, enteral nutrition is instead recommended only after an x-ray examination of the digestive tract with iodized contrast, to verify the correct seal of the anastomosis.

This diagnostic evaluation generally takes place around postoperative day 5–7 in the case of total gastrectomy. In Asia, for selected patients, given good general conditions and the prevalence of initial disease, a diagnostic evaluation after 48 h is allowed, in order to start oral nutrition faster.

## 29.5 Nutritional Follow-Up

In the postoperative period, 1 month after discharge and then every 2–3 months (generally for 1–2 years), a dietary evaluation is required, to monitor and manage any nutritional complications.

### 29.5.1 Nutritional Complications

*Weight loss*: most of the weight is normally lost within 3 months [23]. Beyond this limit, nutritional complications may occur; gastric stasis could give nausea, vomiting, hyporexia and early fullness. The incidence varies from 0.4% to 13%. It can be caused by total vagotomy, hypomotility of the gastric stump in Billroth II surgery, or alterations of jejunal motility in total gastrectomy. Pharmacologic therapy includes prokinetic and antiemetic agents, but good nutritional education is also essential: small and frequent meals as well as liquid and creamy foods are preferred and a reduction in lipid and fiber amount is recommended.

*Dumping syndrome* is a rapid delivery of the bolus into the small intestine, which triggers gastrointestinal and/or vasomotor symptoms and could persist for 1 year. The *early form* is caused by a rapid inflow of hyperosmolar contents into the small intestine, which attract liquids from the intravascular compartment, thus determining distension of the intestinal lumen. It generally occurs 10–30 min after meals and includes gastrointestinal and vasomotor symptoms, such as abdominal pain, nausea, vomiting, diarrhea, headache, flushing, asthenia and hypotension. The *late form* occurs 1–3 h after eating, with predominantly vasomotor symptoms, such as sweating, weakness and confusion. This syndrome is linked to the development of reactive post-surgery hypoglycemia, caused by an abnormal insulin secretion triggered by the rapid glucose absorption into the blood from the intestinal lumen. Eating

small and frequent meals, chewing slowly and frequently, avoiding liquids during meals, limiting the intake of hyperosmolar drinks, increasing fiber intake (which, by increasing viscosity and binding carbohydrates, tends to slow down intestinal transit and glucose absorption) are fundamental recommendations.

*Lipid malabsorption* occurs in 10% of patients. Symptoms (cramping pain and steatorrhea) are caused by decreased gastric lipase, exocrine pancreatic insufficiency, hepatobiliary asynchrony and small bowel bacterial overgrowth. The diagnosis is conducted through fecal fat assay (>7 g in 2 h). Treatment consists in the administration of 500 U/kg of lipase at every meal and half a dose for a snack. Monitoring and supplementation of any fat-soluble vitamin deficiency is required.

### 29.5.2 Nutritional Deficiencies

*Anemia* can be caused by a B12 vitamin, folate or iron deficiency, due to inadequate intake or malabsorption. Anemia must be monitored throughout life and normal levels of B12 vitamin must be maintained (intramuscular supplementation of 1000 μg/month or enteral administration of 1000–2000 μg/day). Despite the limited data available about folate deficiencies, a supplementation of 5 mg/day seems sufficient to correct a folate deficiency. Iron deficiency is corrected with an oral iron administration of 200 mg/day. The iron absorption is improved by vitamin C and amino-acids and inhibited by phytates, phosphates and oxalates.

*Osteopenia* is caused by a decreased calcium intake and/or vitamin D and calcium malabsorption. Current guidelines recommend a daily intake of 1500 mg of calcium and 25-hydroxy vitamin D blood monitoring, trying to keep a blood level of at least 20 ng/mL. For people under the age of 51 years, 600 mg of vitamin D should be sufficient whereas, for people over the age of 71 years, a dose of 8000 mg per day is recommended.

## 29.6 Nutritional Support in Advanced Disease

When malnutrition conditions and intestinal insufficiency impact survival and quality of life more than the disease course itself, nutritional support has the most benefits. For instance, in stage IV gastric cancer patients, it has been observed that the modified Glasgow Prognostic Score and the neutrophil-to-lymphocyte ratio are independent prognostic factors for reduced overall survival [24], highlighting the fundamental role of tumor-induced chronic inflammation. Clearly, in cases of peritoneal carcinosis, parenteral support is preferred because of the higher risk of occlusive events, which contraindicates jejunostomy and oral nutrition. In the case of advanced cardias tumors, during chemotherapy or neoadjuvant therapy a stent placement is indicated, in order to allow oral nutrition and avoid further surgery. In addition, jejunostomy may be indicated [25].

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# ERAS Protocols for Gastrectomy

# 30

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## 30.1 Introduction

Enhanced Recovery After Surgery (ERAS) is a multidisciplinary treatment program for patients undergoing surgery that aims for a fast recovery with a reduction of complications. The interest of upper gastrointestinal surgeons in ERAS is fairly new, and this is demonstrated by the recent publication of the ERAS Society guidelines for gastric cancer and esophageal cancer in 2014 and 2019, respectively [1, 2].

At present, the literature on the application of ERAS protocols in gastrectomy for cancer mainly comes from Eastern countries. Two recently published metanalyses concluded that the use of ERAS in gastrectomy for cancer was associated with a reduction in length of hospital stay, faster bowel recovery and a reduction in costs, but also with a higher risk for readmission [3, 4].

The first Italian experience was conducted by the Italian Group for Research for Gastric Cancer (GIRCG) on seven high-volume centers [5]. This prospective observational study showed that the application of ERAS items was not systematic and was especially low in preoperative and intraoperative items, and for items related to nutritional care.

The aim of this chapter is to describe the key principles of ERAS in gastric cancer patients, focusing on gastrectomy-specific items.

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## 30.2 Preoperative Items

The preoperative items of an ERAS protocol aim at patient optimization prior to the operation and together are defined as *preoptimization*. At present, the evidence on the impact of preoptimization on postoperative outcomes is scarce and based on heterogeneous studies with a variety of interventions, timelines, and outcome measures reported. A recent systematic review of 12 studies focusing on prehabilitation measures in major upper gastrointestinal surgery showed an association between supervised *inspiratory muscle training* (IMT) and a reduction in perioperative morbidity, especially pulmonary complications [6]. A Cochrane metanalysis on 12 randomized controlled trials (RCTs) confirmed the importance of preoperative IMT in patients undergoing major abdominal surgery. Despite the low quality of the included studies, the authors reported a significant reduction in postoperative atelectasis, pneumonia, and length of hospital stay [7].

Preoptimization should include not only physical training but also psychological and nutritional counselling, and should begin as soon as possible. Indeed, it is crucial to consider the impact of a prehabilitation program also on compliance with a possible neoadjuvant treatment. *Nutritional optimization* is a cornerstone in the treatment of patients with gastric cancer, especially in the West. In fact, due to the different incidence and screening programs, Western patients are older, diagnosed at advanced tumor stages and often with accompanying sarcopenia. Malnutrition is a well-established risk factor for postoperative complications, and it can reduce compliance with chemotherapy and even worsen long-term survival. For these reasons a preoperative assessment of the nutritional status by a nutritional team is strongly recommended. The oral/enteral feeding route should be preferred, whenever possible, to parenteral nutrition. Nevertheless, there are currently no clear indications for feeding jejunostomy (FJ) tube placement in gastric cancer patients undergoing neoadjuvant therapy. A retrospective study comparing a high-risk nutritional group of patients with FJ tube placement before treatment with a low-risk group treated with supplementary oral intake showed that the FJ group obtained a significantly higher percentage of chemotherapy completion [8]. FJ tube placement has some drawbacks: it is burdened by a 12.5% morbidity and a 0.5% mortality rate in recent series [9] and, unlike patients that will undergo esophagectomy, FJ cannot be preserved during gastrectomy.

Although the international guidelines advocate the avoidance of prolonged preoperative fasting due to its negative impact on perioperative hydration, it is still a widespread practice to keep patients fasting from clear fluids and food for prolonged lengths of time [10]. Nevertheless, it should be recalled that most of the carbohydrate reserve is consumed at the time of surgery and the subsequent metabolic alteration determines an increase of the catabolic hormones that lead to insulin resistance. For this reason, several studies suggest the positive role of a preoperative *carbohydrate load*. The PROCY trial [11] suggested that a carbohydrate load can be effective in reducing postoperative hyperglycemia and insulin use after major

abdominal surgery, although no significant reduction in postoperative infections was detected.

Several studies have been conducted on the preoperative use of *immunonutrition*, but the results are discordant and the grade of recommendation for its use is low [1, 2].

## 30.3 Intraoperative Items

Gastrectomy is a major abdominal operation with a 30% overall morbidity and a 4.5% mortality [12]. Intraoperative optimization aims to reduce surgical stress by preventing postoperative pain, optimizing oxygen delivery without an extravascular fluid overload, keeping normothermia and avoiding postoperative nausea and vomiting. Despite the importance of *minimally invasive surgery*, we think that it should not be considered as a cornerstone of the ERAS protocol for gastrectomy. Indeed, as discussed in another chapter of this book, laparoscopic surgery is still under investigation for advanced tumors and diffuse histotype forms. Therefore, the protocol must be optimized for both open and laparoscopic approaches.

The anesthetist plays a key role during the operation and should be part of the ERAS team from preoperative assessment to patient discharge. Intraoperative fluid administration is still a matter of debate. A large cohort study reported that both "liberal" and "restrictive" intraoperative fluid management were associated with an increased risk of postoperative complications [13]. Moreover, a multicenter RCT comparing restrictive versus liberal fluid management during and up to 24 h after surgery resulted in an increased rate of acute kidney injury without any advantage in other complications in the restrictive group [14].

An attempt to optimize oxygen delivery to match the metabolic requirement of a patient undergoing major surgery is based on *goal-directed hemodynamic and fluid therapy* (GDT). This is a tailored fluid approach driven by minimally invasive devices monitoring the stroke volume variation and the pulse pressure variation integrated with derivative monitoring systems of cardiac output and cardiac index. If necessary, after preload optimization through fluid administration, the anesthetist should proceed with the use of a vasopressor to obtain adequate tissue perfusion (preoperatively established based on patient clinical conditions). GDT has been already recommended for high-risk patients in the international guidelines and encouraging results come from an RCT on low-to-moderate risk patients in which the GDT group obtained a reduction in overall complications and length of stay [15].

*Multimodal analgesia* combining non-opioid analgesics and locoregional/neuraxial techniques is a cornerstone of the ERAS pathway. The best approach should be tailored based on the surgical incision and possible contraindications due to the patient's comorbidities.

In open gastrectomy, thoracic epidural analgesia (TEA) with local anesthetics and opioids is still considered a key analgesic component of pain treatment as it has

been associated with a decreased postoperative opioid consumption and a reduction in pulmonary complications, compared with patients without TEA [16]. Unfortunately, TEA is burdened by some possible drawbacks in the postoperative period, such as orthostatic hypotension and urinary retention and has a small percentage of serious complications. Moreover, it is contraindicated in certain patients and therefore a standardized alternative should be planned. In these patients transversus abdominis plane (TAP) block and rectus sheath (RS) block use should be considered as they demonstrated to be superior compared with intravenous exclusive analgesia [17]. As the benefits evidenced with the use of TEA have not been observed after laparoscopic procedures, especially within an ERAS program, a different strategy should be implemented in these patients. TAP and RS blocks demonstrated a reduction in postoperative opioid consumption and therefore should be considered. Nevertheless, it has to be remembered that the analgesia provided by these techniques is based on the direct peripheral nerve blockade and therefore does not cover visceral pain. Lastly, wound infiltration with local anesthetic, including the trocar access site for laparoscopy and robotic techniques, can be considered, even though less effective than the previously described interfascial plane blocks [18].

## 30.4 Postoperative Items

Postoperative management requires the cooperation of multiple figures: anesthetist, nurse, nutritionist, physiotherapist, surgeon and, above all, the patient. Indeed, the patient's cooperation is essential to achieve excellent results, and this can be obtained only by continuous perioperative counseling. A recent RCT on colorectal surgery reported that extensive perioperative counseling with dedicated nurses that supervised the whole patients' pathway can lead to a shorter length of stay with improved compliance [19].

Starting before the operation, *multimodal analgesia* should continue during the hospitalization. Several tools are available for pain detection, such as the NRS (numerical rating scale) and VAS (visual analog scale), and a systematic recording of pain is mandatory. Multimodal analgesia should give adequate 24 h pain relief with a defined protocol for breakthrough pain, possibly using patient-controlled analgesia systems.

Following the indications provided for intraoperative fluid management, the postoperative goal for intravenous fluid infusion should be based on maintaining normovolemia and resuming the enteral/oral route as soon as possible. Avoidance of the intensive care unit and invasive monitoring requires increased attention of ward/step-down unit nursing and medical staff in the early postoperative period. Hemodynamic variables such as heart rate and blood pressure, hourly diuresis,

serum concentration of lactates and weight modification are simple but effective predictors of fluid balance and correlate with postoperative outcome.

Patients treated with TEA may require a larger amount of intravenous fluid to compensate for the vasodilation induced by the reduction of sympathetic tone; in these patients a low dose of vasopressor may be considered to maintain an adequate organ perfusion. For this reason, minimally invasive surgery associated with TAP and RS blocks may improve postoperative fluid management.

Postoperative surgical items in an ERAS pathway should follow the concept of "less is more". And this is especially true for upper gastrointestinal surgery, where classical practices not supported by scientific evidence, such as the use of a decompressive tube (DT), prophylactic drain (PD), and prolonged fasting, are still widely used.

Postoperative use of a DT aims to improve gastric/jejunal decompression, thus reducing aspiration pneumonia and anastomotic leak. However, a recent meta-analysis [20] reported a comparable incidence of anastomotic leak, pulmonary complications and overall mortality between patients with or without a DT after gastrectomy. Moreover, an Italian RCT from the GIRCG highlighted how patients with DT complained of discomfort, pharyngeal irritation, otitis and sinusitis, with a comparable need for re-insertion of the tube due to delayed gastric/jejunal emptying (10%) [21].

Similarly, the use of a PD on the anastomosis and duodenal stump has been questioned in the last 15 years, but to date only few studies with a small sample size have been published. In 2020 an up-to-date meta-analysis compared the use or avoidance of a PD after gastrectomy for cancer [22]. No differences between the two groups were found in terms of morbidity and mortality, while a significant reduction in length of hospital stay in favor of the no-drain group was noted. Nevertheless, it has to be highlighted that this evidence comes mainly from Eastern countries and from small series. At present, PD use is discouraged by the ERAS Society guidelines [1] but further studies are needed.

Several trials focusing on an *early resumption of oral intake* (starting from postoperative day 1) concluded that this practice is safe and effective in reducing postoperative ileus [23, 24]. Moreover, nasogastric tube avoidance and early resumption of oral intake have been associated with a reduced rate of delayed gastric emptying [25] and patient discomfort, leading to faster nutritional recovery, mobilization and discharge. Table 30.1 summarizes the main pre-, intra- and postoperative items in an ERAS protocol.

Discharge should be planned according to predefined *discharge criteria* and to the patient's network. These criteria should include autonomy in mobilization, pain controlled by oral analgesics, tolerability of oral nutrition and/or enteral nutrition of at least 60% of the daily target requirement. Systematic audit within the ERAS team should be carried out on a monthly basis.

**Table 30.1** ERAS protocol: items for gastrectomy

| | |
|---|---|
| Preoperative | |
| Counseling | Pathway explanation and informative booklet. Nutritional counseling and IMT |
| Preoperative fasting | Carbohydrate load 12 and 2 h before surgery |
| Intraoperative | |
| Analgesia | Multimodal: TEA for open surgery; TAP + RS block for laparoscopic surgery or if TEA contraindication + CNS targeted drugs |
| Prophylaxis | Antibiotic prophylaxis, VTE (pharmacological and mechanical), PONV prophylaxis + active warming |
| Fluids | Goal-directed fluid management |
| Extubation | Immediate extubation |
| Hospital acuity | Ward or PCU for close monitoring |
| NGT | Remove at the end of surgery |
| Postoperative | |
| Analgesia | Multimodal: TEA; fixed time interval-opioid sparing analgesia + rescue therapy with NSAIDs or codeine. Prefer PCA if available |
| Fluids | Zero balance goal; switch to oral/enteral intake when tolerated |
| Abdominal drain | Avoid drain if no intraoperative concerns. Remove as soon as possible |
| Line management | Remove urinary catheter in POD 1 if adequate urine output and preserved renal function |
| Diet | Early resumption of oral intake (starting from POD 1), nutritional counselling |
| Rehabilitation | Early mobilization, IMT, passive and active physiotherapy (POD 0/POD 1) |
| Length of stay | Discharge should be based on safety criteria (timed discharge) |

*IMT* inspiratory muscle training, *TEA* thoracic epidural anesthesia, *TAP* transversus abdominis plane, *RS* rectus sheath, *CNS* central nervous system, *VTE* venous thromboembolism, *PONV* postoperative nausea and vomiting, *PCU* progressive care unit, *NSAIDs* nonsteroidal anti-inflammatory drugs, *NGT* nasogastric/jejunal tube *PCA* patient-controlled analgesia, *POD* postoperative day

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# Complications After Gastrectomy for Cancer

# 31

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## 31.1 Introduction

The mainstay of therapy for gastric cancer remains radical surgery with lymphadenectomy. In Western countries, gastrectomy is currently performed in hospitals with variable case volume, as centralization of gastric cancer surgery has not been widely accepted. Consequently, the postoperative mortality rate (3–5%) is surprisingly high, when compared to Eastern countries [1, 2]. Postoperative morbidity rates are less homogenous, because published series use inconsistent descriptive terminology. As a result, studies have reported a wide range of major morbidity rates, from 11% to 46% [3–6].

Postoperative complications have major impacts on short- and long-term outcomes, both from the oncological and from the quality-of-life point of view. It is of paramount importance to record, classify and analyze the postoperative courses in a standardized way. The final goal would be the detection and correction of risk factors, so as to improve the final morbidity and mortality rates [7].

The first step in this direction is establishing a common language ensuring consistency in the definitions of gastrectomy complications. Many studies already

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showed the benefits of standardized reporting, when comparing the differences between Western and Eastern clinical outcomes [8]. To address this issue, in November 2015 a group of European gastric cancer experts, members of the International Gastric Cancer Association (IGCA), launched a project aimed to define a comprehensive list of surgery-related and gastric cancer-specific complications; adverse events included in this list were deemed essential items to be included in multicenter studies and international databases. A similar important and pioneering study was performed by Low and colleagues in the field of esophageal surgery [9].

## 31.2 The European Gastric Cancer Association Project

The project "Complications after gastrectomy for cancer. European perspective" included 31 surgeons from 13 European countries, as part of the Gastrectomy Complications Consensus Group (GCCG); the volume of gastric cancer surgery, the availability of a data collection system, and a proven scientific interest in the field were minimum requirements to take part in the project. After 10 rounds of an online Delphi consensus survey (660 answers were analyzed, with a mean of 21 [range 11–36] answers from each participant) and 4 meetings in 2017 and 2018, a standardized list comprising 27 perioperative complications associated with gastrectomy was developed and published [10]. Despite disagreement on some questions, the Delphi survey delivered a strong consensus on the most critical issues. A great effort was devoted to agreement on the definition of each complication. The definitions were kept precise but simple and focused on the critical features of each clinical scenario. The list of complications is reported in Table 31.1. This project represented a starting point for generating a wider international consensus for standardization of data collection for cancer-related gastric resection.

In the next step of the project, which was run in 2019, an electronic application-based Complications Recording Sheet was developed, with the aim of assessing the incidence of these complications across specialized European centers. A benchmark for complications was searched for. A secure web-based platform (www.gastrodata.org) was developed to allow uniform data collection. The GCCG members provided the critical input for building the platform, which was then carefully tested with a few retrospective and prospective cases for each center before its official launch in early 2019.

In 2017 and 2018 a retrospective observational study was set up, including all consecutive resections for gastric cancer performed at participating European centers, according to the STROBE guidelines and checklist [11].

The primary endpoints of this study were as follows: (1) incidence and grading of the 27 perioperative complications; (2) number and type of re-interventions; (3) number of hospital re-admissions; (4) mortality (total and cause-specific) during hospital stay and at 30 days and 90 days postoperatively; (5) blood product utilization; and (6) escalation in level of care.

**Table 31.1** Gastrectomy for cancer: the list of complications

| | |
|---|---|
| *Intraoperative complications* | |
| 1. | Unintended intraoperative damage to major vessels and/or organs requiring reconstruction or resection |
| 2. | Intraoperative bleeding requiring urgent treatment |
| 3. | Unexpected medical conditions interrupting or changing the planned procedure |
| *Postoperative general complications* | |
| 4. | Stroke causing patient's permanent deficit |
| 5. | Need for CPR |
| 6. | Myocardial infarction with patient's transfer to CCU/ICU/other critical care facility |
| 7. | Cardiac dysrhythmia requiring invasive treatment |
| 8. | Acute myocardial failure with acute pulmonary edema or drop in EF >50% |
| 9. | Pulmonary embolism with symptoms confirmed by urgent CT scan |
| 10. | Respiratory failure requiring reintubation |
| 11. | Need for tracheostomy |
| 12. | Pleural effusion requiring drainage |
| 13. | Pneumothorax requiring treatment |
| 14. | Need for prolonged intubation (>24 h after the surgical procedure) |
| 15. | Acute liver dysfunction (Child-Pugh score >8 for longer than 48 h) |
| 16. | Acute renal insufficiency (postoperative creatinine twice its preoperative value)/renal failure requiring CVVH or dialysis |
| 17. | Infections (gastrointestinal, respiratory, urinary, or other) with both symptoms and germ isolation |
| *Postoperative surgical complications* | |
| 18. | Postoperative bleeding requiring both urgent transfusions and invasive treatment |
| 19. | Postoperative bowel obstruction (clinical/radiological signs of obstruction, inability to feed enterally, longer need for NG suction) |
| 20. | Postoperative bowel perforation or necrosis requiring surgical treatment (or cause of death) |
| 21. | Duodenal leak (irrespective of presentation, method of identification, clinical consequences, and treatment) |
| 22. | Anastomotic leak (irrespective of presentation, method of identification, clinical consequences, and treatment) |
| 23. | Postoperative pancreatic fistula |
| 24. | Postoperative pancreatitis diagnosed both clinically and radiologically |
| 25. | Other postoperative abnormal fluid from drainage and/or abdominal collections without gastrointestinal leak(s) preventing drainage removal or requiring treatment |
| 26. | Delayed gastric emptying (by 10th postoperative day) requiring treatment or delaying discharge |
| 27. | Other major complications requiring re-intervention or other invasive procedures |

All complications occurring during the in-hospital stay and within 90 days after surgery should be included and recorded in the Complications Recording Sheet for each patient episode. *CPR* cardiopulmonary resuscitation, *CCU* coronary care unit, *ICU* intensive care unit, *EF* ejection fraction, *CVVH* continuous venovenous hemofiltration, *NG* nasogastric

This important study included 1349 patients (median patient episodes per center was 47). A typical Western population was described: patients were predominantly >70 years old, overweight, and with various comorbidities. Young patients with BMI <20 kg/m$^2$, ASA score 1, and a Charlson Comorbidity Index 0 were less than 10% of the study population. The same was evident from an oncological point of view: half of patients had lost weight, 60% had T3/T4 cancer, while only 20% of patients had early gastric cancers; the proximal localization of the tumor or linitis

plastica was reported in 60% of cases, against an average of 30% in the Eastern series. Finally, 80.2% of patients in this series underwent open surgery, and 79.7% underwent D2 or D2+ lymphadenectomy.

A total of 402 patients (29.8%) developed at least one complication (overall, 625 episodes of complication were reported). A Clavien-Dindo grade ≥ 3 was reported in 63.9% of complicated cases. Surgical re-intervention was necessary in 105 cases (7.8%) and transfer to the ICU in 84 cases (6.2%). Mortality rates were 3.2% during the hospital stay, 3.6% at 30 days postoperatively, and 4.5% at 90 days postoperatively. Intraoperative complications were rare (about 2% of cases). The most frequent complications were non-surgical infections (23%), anastomotic leak (9.8%), other postoperative abnormal fluid from drainage and/or abdominal collections without gastrointestinal leak(s) (9.3%), pleural effusion requiring drainage (8.3%), postoperative bleeding requiring urgent transfusions or invasive treatment (5.6%).

These data are significantly different from those reported by Eastern centers, where mortality rates are always lower or around 1%. Beyond the likely differences in histological features and patient-related risk factors, there may be notable differences pertaining to surgical, and hence, improvable, factors. Understanding the factors associated with these higher mortality and morbidity rates is thus critical. Actions toward quality improvement of the surgical techniques seem mandatory. Prominent international scientific organizations, as well as medical institutions, should clearly play a major role on this issue [12].

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# Long-Term Survival and Follow-Up After Gastrectomy for Cancer

# 32

Maurizio Degiuli, Gian Luca Baiocchi, Lucia Puca, and Rossella Reddavid

## 32.1 Follow-Up: Introduction

At present, there is no definitive evidence supporting the practice of imaging follow-up after gastrectomy for cancer: many retrospective series clearly state that diagnosis of tumor recurrence in asymptomatic patients does not improve survival, compared to late diagnosis [1–3]. However, in most high-volume centers patients undergo repeated clinical and imaging assessments in the 3 to 5 years after surgery [4]. The conflict between theory and practice is evident in this field. A scheduled follow-up of asymptomatic patients may offer some clinical benefit, but should be critically re-evaluated in this period of limited resources, by identifying tests and examinations with the best reliability and sensitivity, by limiting them to a period of time when recurrence is likely and concentrating clinical efforts and expenditures on those recurrences whose diagnosis may translate into a cancer-directed therapy.

High-grade evidence on this topic is unlikely to be provided by randomized controlled trials (RCTs), thus the strongest evidence achievable was provided by an expert consensus.

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## 32.2 Follow-Up: The Charter Scaligero

In June 2013 in Verona (Italy), during the 10th International Gastric Cancer Congress (IGCC) organized by the Italian Research Group for Gastric Cancer, a Consensus Conference entitled "Rationale of oncological follow-up after gastrectomy for cancer" took place, with the ultimate goal of producing a consensus paper, the Scaligero Charter. The aim of this paper was to present an ideal prototype for follow-up, based on shared experiences and taking into account the need to rationalize the diagnostic course while not missing the chance to detect a recurrence at its earliest stage. Other factors to be considered were: psychological stress induced by useless tests; cost-benefit ratio of imaging examinations; side effects of invasive diagnostic procedures; possibility of causing a premature "diagnosis of death".

A restricted working group was established to review the literature, find unsolved issues, and share a proposal statement for each issue; 48 experts including surgeons, oncologists, radiation oncologists, gastroenterologists, statisticians and methodologists agreed to participate in an extended working group which, according to the dictates of the Delphi method, reached a final consensus. International experts were selected with a geographical distribution reflecting different health cultures worldwide, therefore from both "emerging" and highly developed countries [5]. Six statements were approved, displayed in the plenary session and endorsed by the vast majority of the 10th IGCC participants, and were therefore published in 2015 [6].

The Consensus Conference finally supported the practice of following-up patients by imaging examinations after gastrectomy, for the following reasons: oncological (detection and management of cancer recurrence), gastroenterological (endoscopic surveillance and management of post-gastrectomy symptoms), research (collection of data on treatment toxicity, time to and site of recurrence, survival, and cost-benefit analyses), and pastoral (psychological and emotional support) [6]. Other important topics raised by the Charter Scaligero were:

1. Follow-up should include lifetime monitoring of the nutritional sequelae of gastrectomy, including, but not limited to, adequate vitamin B12, iron, and calcium replacement.
2. Follow-up should be tailored to the individual patient, to the stage of their disease, and to the treatment options available in the event that recurrence is detected.
3. A follow-up program intended to detect asymptomatic recurrence should be based on cross-sectional imaging.
4. Upper gastrointestinal endoscopy may be used to detect local recurrence or metachronous primary gastric cancer in patients that have undergone a subtotal gastrectomy.
5. Routine screening for asymptomatic recurrence of gastric cancer may be discontinued after 5 years, as recurrence beyond that interval is very rare.

Data on long-term survival are reliable only if a true follow-up is available. The Italian Research Group for Gastric Cancer (GIRCG) regularly subject patients to post-surgical follow-up for 5 years and in some cases up to 10 years. The results are shown in Figs. 32.1, 32.2, 32.3 and 32.4. This way, the following subgroups of treated patients should be classified.

## 32.3 Long-Term Survival in Early Gastric Cancer

General guidelines for selecting patients with early gastric cancer (EGC) who are appropriate for curative endoscopic resection are primarily based upon the risk of lymph node (LN) metastases observed in surgical resections [7]. Patients meeting Gotoda's standard criteria could safely undergo endoscopic mucosal resection (EMR) because they are expected to be free from LN metastases [8]. Expansion of the criteria was proposed by centers from Eastern Asia, but endoscopic submucosal dissection (ESD) still remains under evaluation and patients meeting expanded criteria should be considered only for experimental trials and restricted to centers of excellence. These patients have a good prognosis with survival rates close to 100%, whereas the 5-year cumulative incidence of recurrent gastric cancer is estimated to be from 2.9% to 14% [9]. A potential risk of distant metastasis after endoscopic resections remains because LN dissection is not performed in these procedures.

ECG patients who have risk factors for LN metastasis after endoscopic resection or those who do not meet the Gotoda criteria must undergo surgery with D1 or D1 plus lymphadenectomy, according to their characteristics [7]. Large European RCTs comparing survival after D1 or D2 gastrectomy for gastric cancer did not report significant differences in 5-year disease-specific survival (DSS) in stage I patients [10]. Nonetheless, surgery with adequate lymphadenectomy offers a high probability of cure, with reported long term DSS >90%.

Despite the overall good prognosis of EGC, some subtypes show a significantly worse oncologic outcome. In 2006 the GIRCG retrospectively analyzed 652 cases of resected EGC and established that submucosal invasion, Laurén diffuse/mixed type, Kodama Pen A type and tumor size are associated with an increased risk of LN metastases [11]. For these reasons, the GIRCG guidelines advise D2 lymphadenectomy in ECG not suitable for endoscopic treatment [12].

## 32.4 Long-Term Survival in Advanced Gastric Cancer

Today, a D2 procedure is recommended as the standard surgical treatment for resectable advanced gastric cancer (AGC) by several guidelines of surgical and medical Western societies. More recently, the NCCN recommended D2 resection also in the United States. Survival outcomes of patients undergoing upfront surgery with adequate LN dissection for AGC are similar in both Eastern and Western countries, the 5-year overall survival for AJCC stage II and III ranging from 44% to 86% and from 22% to 64% respectively [13].

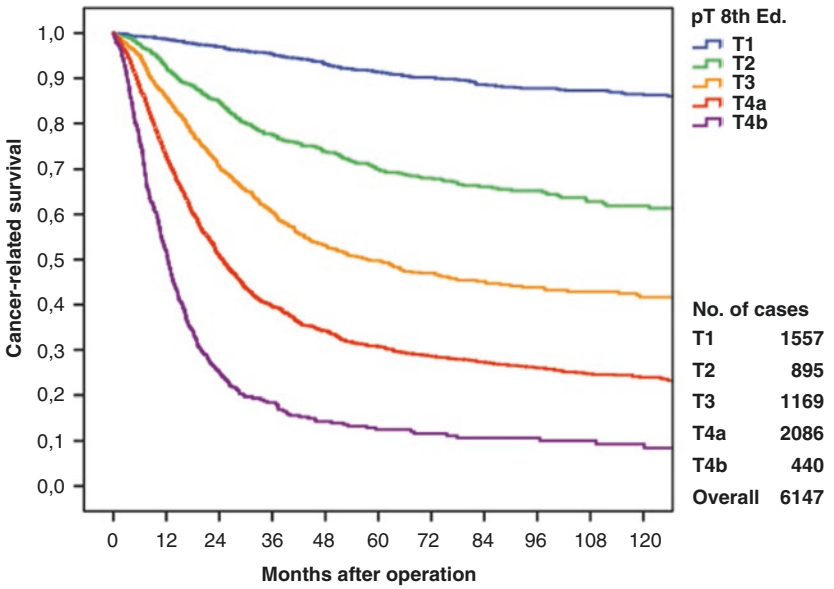


**Fig. 32.1** Gastric cancer-related survival according to UICC pT stage (8th edition) in 6147 patients operated on in 10 Italian centers between 1994 and 2015. Survival function is calculated according to the Kaplan-Meier method. (Data source: Italian Research Group for Gastric Cancer (GIRCG) database. Data processing: University of Siena)

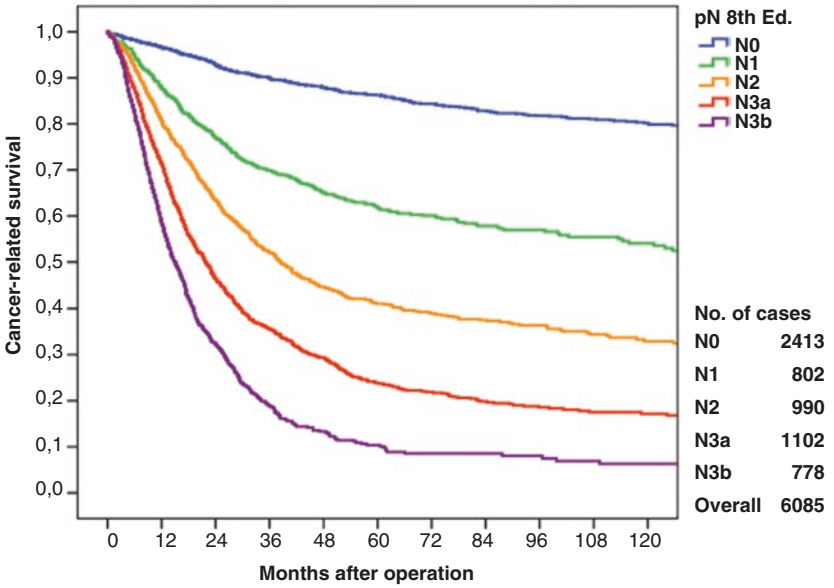


**Fig. 32.2** Gastric cancer-related survival according to UICC pN stage (8th edition) in 6085 patients operated on in 10 Italian centers between 1994 and 2015. Survival function is calculated according to the Kaplan-Meier method. (Data source: Italian Research Group for Gastric Cancer (GIRCG) database. Data processing: University of Siena)

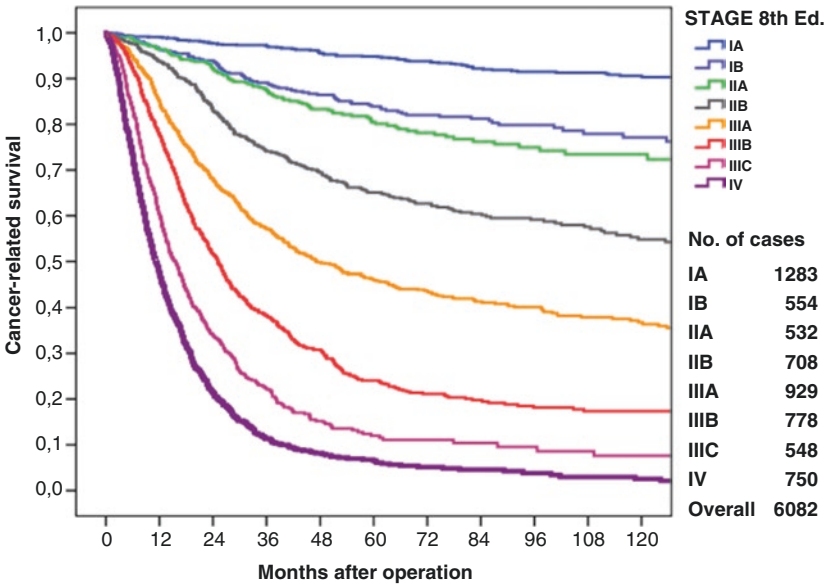


**Fig. 32.3** Gastric cancer-related survival according to UICC stage groups (8th edition) in 6082 patients operated on in 10 Italian centers between 1994 and 2015. Survival function is calculated according to the Kaplan-Meier method. (Data source: Italian Research Group for Gastric Cancer (GIRCG) database. Data processing: University of Siena)

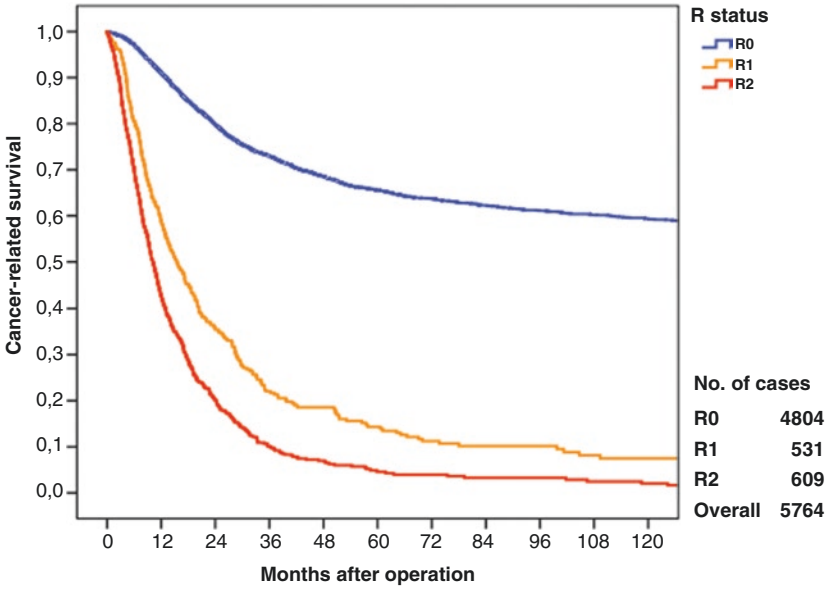


**Fig. 32.4** Gastric cancer-related survival according to surgical radicality (R status) in 5764 patients operated on in 10 Italian centers between 1994 and 2015. Survival function is calculated according to the Kaplan-Meier method. (Data source: Italian Research Group for Gastric Cancer (GIRCG) database. Data processing: University of Siena)

In recent times, a multimodal approach to resectable AGC with the adoption of neoadjuvant (preoperative or perioperative) treatment has been introduced in several national guidelines, particularly after the publication of the MAGIC and French randomized controlled trials (RCTs). However, its appropriateness is debated owing to the lack of strong evidence of its survival benefit as compared to upfront surgery alone with proper D2 dissection in patients with stomach cancers [14]. Recently, a new safe and effective neoadjuvant regimen, a docetaxel-based combination consisting of fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT), has been recommended with a significant improvement of survival outcomes compared with previous ECF-based regimens (epirubicin, cisplatin, and fluorouracil), with 3- and 5-year overall survival rates of 57% and 45%, respectively [15].

## 32.5 Long-Term Survival in Far Advanced Gastric Cancer

Chemotherapy remains the main therapeutic approach for stage IV gastric cancer. Unfortunately, median survival time of these patients remains low, ranging from 3 to 16 months. The role of gastrectomy is unclear in far advanced gastric cancer (FAGC) patients, reduction surgery aiming to prolong survival and/or to delay the onset of symptoms by reducing tumor volume [7]. An international cooperative RCT showed that these patients can benefit from surgery in terms of survival only when it is radical.

Few stage IV non-resectable gastric cancers can become resectable after neoadjuvant treatment, and several studies have reported that conversion surgery for unresectable stage III or stage IV gastric cancer is associated with survival ranging from 37 to 56 months, significantly longer than after chemotherapy alone. This procedure is a treatment option for selected patients with stage IV gastric cancer and, when radical, it is significantly associated with a reduced risk of recurrence. The main negative prognostic factor is the presence of more than one type of extra-gastric metastatic involvement.

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# Part VI

# Technical Notes in Gastric Surgery [Video Content]

# Open D2 Lymphadenectomy

# 33

Paolo Morgagni and Massimo Framarini

## 33.1 Introduction

D2 lymph-node dissection is currently the standard for curative-intent gastrectomy as required by all the European guidelines; lymph node collection by stations according to the Japanese classification of gastric carcinoma [1] during surgery or on the surgical specimen can be performed by either the pathologists or the surgeons (Fig. 33.1): this is essential in order to evaluate the real compliance to D2 dissection.

Another important technical aspect of D2 lymphadenectomy is the use of surgical devices that seal all the lymphatic channels in order to avoid lymphatic spillage [2] during surgical dissection.

## 33.2 Lymph Node Dissection for a D2 Lymphadenectomy During Gastrectomy

En-bloc dissection of perigastric lymph nodes must be preferred and resection of the gastric and gastroepiploic vessels must be performed at their root. The left paracardial lymph nodes (station 2) must be removed only during total gastrectomy.

Dissection of second-tier nodes (stations 8a, 9, 11p, 12a), can be more easily performed intraoperatively during the different phases of the surgical procedure. Lymph nodes at the splenic hilum (station 10) and distal splenic artery (station 11d) must be removed only after total gastrectomy.

**Supplementary Information** The online version of this chapter (https://doi.org/10.1007/978-3-030-73158-8_33) contains supplementary material, which is available to authorized users.

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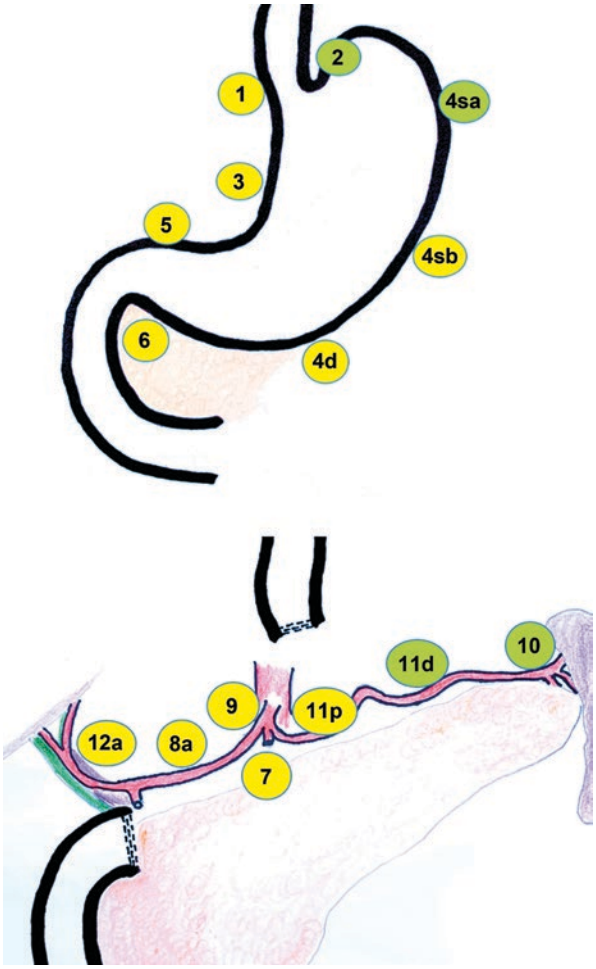


**Fig. 33.1** Stations considered for D2 dissection in subtotal gastrectomy (*yellow*) and in total gastrectomy (*yellow and green*)

Starting from the hepatic hilum, the hepatoduodenal ligament dissection is completed by removing lymph nodes along the hepatic artery, common bile duct, as well as the anterior periportal lymph nodes. Then, the lymphadenectomy along the celiac artery (station 9) is performed, and finally the lymph nodes at the origin of the splenic artery (station 11p) are removed.

Splenectomy is not required except in cases of locally advanced tumors of the upper-third stomach located along the greater curvature: in such cases, the lymph nodes of the distal splenic artery (station 11d) and of the splenic hilum (station 10) are removed.

## 33.3 How to Prepare Specimens After Total Gastrectomy

Dissection of the first seven lymph-node stations can be easily undertaken on the resected stomach if the right and left gastroepiploic vessels, the vasa brevia, the right and left gastric vessels are marked with suture material.

First, the great omentum is dissected at a distance of 2 or 3 cm from the gastroepiploic vessels (stations 4sa, 4sb, 4d). Then the left gastric artery with the surrounding adipose tissue is sectioned near to the gastric wall (station 7).

The right and left paracardial lymph nodes (stations 1 and 2), the lymph nodes of the lesser curve (station 3) and finally the supra- and infrapyloric lymph nodes (stations 5 and 6) are removed. All the adipose tissue surrounding the stomach is thus removed, and the gastric wall from the cardias to the pylorus is exposed.

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# Laparoscopic D2 Lymphadenectomy

# 34

Simone Giacopuzzi

In this video chapter we show the main steps for a D2 lymphadenectomy. The surgeon and the assistant stand on the right and left side of the patient, respectively, and they can change their position according to the surgical steps. The camera operator stands between the patient's legs. We use four ports with an additional one to retract the liver, the trocar placement follows a V-shaped line having its tip on the umbilicus.

The operator and the assistant form a triangle to properly expose the gastrocolic ligament and avoid injury to the transverse mesocolon. The assistant lifts up the stomach with the right hand while with the left hand the pulls the omentum down to the left side. The section of gastrocolic ligament begins 4–5 cm from the greater curvature of the stomach, from the right to the left side in order to open the bursa omentalis up to the left gastroepiploic vessels, so stations 4sb and 4d are retrieved.

In total gastrectomy, we dissect the short gastric vessels and divide the greater curvature of the stomach from the spleen up to the left side of the cardias to clear lymph node stations 4sa and 2.

The dissection continues toward the right side, between the transverse mesocolon and the omentum, up to the origin of the right gastroepiploic vein; this part of dissection is more challenging. The assistant lifts up the posterior wall of the antrum and retracts medially the transverse mesocolon. The root of the right gastroepiploic vein and artery will be exposed sectioned at the level of pancreatic head, the lymphatic tissue of this area cranial to the anterior-superior pancreaticoduodenal vein should be dissected: the infrapyloric lymph nodes of station 6 are so removed.

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The next step is the dissection of right gastric artery with the removal of station 5 lymph nodes. The assistant simultaneously pushes down the anterior wall of the stomach and raises the lesser omentum, so that the operator can isolate and dissect the right gastric artery. The duodenum is then transected.

At this point, the assistant lifts up the gastro-pancreatic fold and rolls down the pancreas with a gauze. All the lymphatic tissue along the cranial border of the pancreas is removed visualizing the "U" shape line on the right side of the left gastric artery, above the hepatic artery, and the "V" shape line on the left side of the left gastric artery, along the splenic artery. During the suprapancreatic dissection, stations 8a, 9, 11p, and 7 are sequentially dissected and removed en bloc.

To complete the D2 lymphadenectomy the anterior lymph nodes of the hepatoduodenal ligament (station 12a) are dissected. Of note, to properly complete dissection of station 12a, the portal vein should be visualized.

In the case of total gastrectomy, the procedure ends with dissection of the distal splenic artery lymph nodes (station 11d).

Instead, the last step for subtotal gastrectomy is represented by dissection and removal of the lesser curvature (station 3) and right paracardial (station 1) lymph nodes, from the right side of the cardias to the lesser curvature.

# Open D3 Lymphadenectomy

# 35

Giovanni de Manzoni

According to the Japanese classification of gastric carcinoma [1], lymph nodes in the para-aortic region are divided into four nodal stations based on specific anatomic landmarks:

- *station 16a1* in the diaphragmatic aortic hiatus;
- *station 16a2* between the upper margin of the origin of the celiac artery and the lower border of the left renal vein;
- *station 16b1* between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery;
- *station 16b2* between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation.

Para-aortic node dissection (PAND) for gastric cancer includes the removal of nodal stations 16a2 and 16b1.

Extended D3 lymphadenectomy involves mobilization of the duodenum with the Kocher maneuver: specifically, the assistant retracts the second duodenal portion in order to expose the parietal peritoneum. The operator then cuts the parietal peritoneum near the lateral edge of the descending portion of the duodenum. Continuing the peritoneal section, the assistant medially rotates the duodenum and the dissection continues until the pancreatic head is mobilized. This provides access to the para-aortic node stations as well as improving the surgical exposure of lymph node

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stations 8p, 12p, and 13. PAND consists in the retrieval of lymph nodes between the upper margin of the origin of the celiac artery and the lower border of the left renal vein (station 16a2) with lymph nodes between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery (station 16b1).

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# Robotic D3 Lymphadenectomy

# 36

Franco Roviello, Riccardo Piagnerelli, and Luigi Marano

The patient lies in a supine, split-leg, 15° anti-Trendelenburg and 15° left-tilted position, with both arms tucked along the body.

After the induction of general anesthesia, pneumoperitoneum is established using a Verres needle technique. A periumbilical 12 mm trocar is positioned on the left spinoumbilical line, and the 30° high-definition 3D robotic camera is introduced. Under direct vision, two 8 mm robotic trocars are placed, one in the upper abdomen at the midclavicular line on the left (robotic arm 1) and one in the lower abdomen on the right, at the crossing of the right midclavicular line and the right spinoumbilical line (robotic arm 2). In addition, a 12 mm port for the assistant is placed in the hypogastric region, 2 cm to the left of the midline.

At the time of trocar positioning, the first surgeon stands on the patient's right side and the first assistant on the patient's left. After trocar insertion and robot docking, the first assistant stands on the patient's left side; a second assistant surgeon can stay on the patient's right side, near the robotic high-definition monitor. The robotic cart comes up from the right shoulder. The instruments used are: a monopolar curved scissors installed on robotic arm 1, a fenestrated bipolar forceps on robotic arm 2. The assistant port is used for irrigation/suction, clip applying and for better exposure of the surgical field.

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We divided the procedure into four steps, as follows:

1. *Right colonic flexure mobilization*. The right colon is mobilized with a lateral-to-medial traction, the hepatic flexure is freed and the Toldt plane exposed.
2. *Kocher maneuver*. Once the right flexure is completely freed, the duodenum is mobilized with both blunt and sharp dissection (R1). This provides access to the interaortocaval space until the exposure of the left renal vein (LRV) and the aorta. The right gonadic vein is also exposed.
3. *Lower interaortocaval nodal harvesting*. This phase implies the resection of lymph nodes between the LRV and the IMA (station 16b1). This area is completely cleared from all the lymphatic tissue, paying attention to cleaning the space within the LRV and the origin of the right renal artery (RRA).
4. *Upper interaortocaval nodal harvesting*. After the complete resection of the lymph nodes in the lower interaortocaval space, attention is shifted to the area between the celiac trunk (CT) and the upper margin of the LRV (station 16a2), harvesting all the lymph nodes in this space.

Phases 3 and 4 are performed using both blunt and sharp dissection with R1, bipolar coagulation with R2, and clip applying by the assistant trocar for the lymphatic vessels, together with irrigation and suction in order to expose the surgical field as clearly as possible.

Once hemostasis is achieved, we proceed with a redocking of the robotic cart in order to start the total gastrectomy. At the end of the procedure, drainage is placed in the interaortocaval area.

# Minimally Invasive Reconstruction in Total Gastrectomy

# 37

Lavinia Barbieri, Eider Talavera-Urquijo, Paolo Parise, Andrea Cossu, Francesco Puccetti, Ugo Elmore, and Riccardo Rosati

Reconstruction of the alimentary tract after laparoscopic total gastrectomy is performed with a Roux-en-Y esophagojejunostomy, in antecolic fashion unless the presence of a short mesentery requires a transmesocolic route. The camera is inserted above the umbilicus and total gastrectomy plus D2 lymphadenectomy is performed with three other operating ports. The jejunum is divided 20 cm distally to the Treitz ligament with a linear stapler (Ethicon Echelon 60-mm, vascular cartridge); with the aid of an energy device and clips, the mesentery is dissected as much as needed for the jejunum to reach the esophagus without tension. We prefer to begin the reconstruction with a jejunojenunal laterolateral anastomosis: each jaw of the linear stapler (Ethicon Echelon 60-mm, white cartridge) is inserted into the jejunum through a small enterotomy on the antimesenteric surface of the bowel. The stapler is fired and extracted. After checking for the absence of bleeding, the enterotomy is closed with a running barbed absorbable 3.0 suture and the mesentery is closed in the same way.

We then turn to the alimentary tract. The distal esophagus is dissected upwards, clearing its abdominal and lower mediastinal tract; both vagal nerves are divided to obtain tension-free stability of the esophagogastric junction (EGJ) inside the abdomen. Then, the jejunal limb is pulled up and aligned with the distal esophagus. The nasogastric (NG) tube is retracted up to the mediastinal esophagus. Two small holes are made on the right dorsal side of the esophagus, just above the EGJ, and

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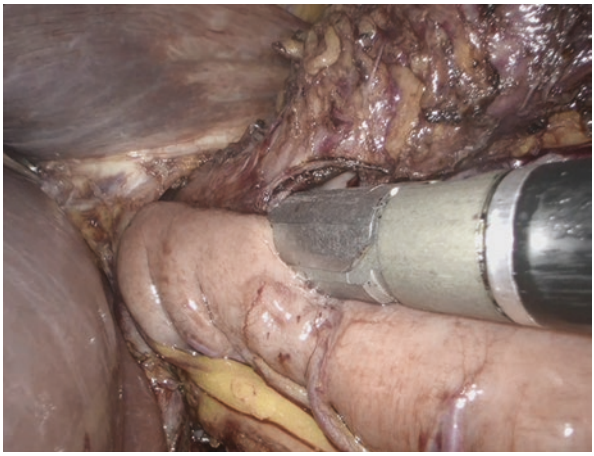

**Fig. 37.1** Esophagojejunal anastomosis. Each jaw of a linear stapler is inserted in the jejunal and esophageal stump to create the laterolateral anastomosis. Then, another application of the liner stapler is used to transect the esophagus and close the common enterotomy

approximately 6 cm distal to the end of the jejunal stump, on the antimesenteric surface. The jaws of the linear stapler (Ethicon Echelon 60-mm, blue cartridge) are inserted and the esophagojejunostomy is fashioned (Fig. 37.1). The esophagus is transected with a further oblique application of a linear stapler of the same kind and the anastomosis is completed with interrupted monofilament absorbable 3.0 suture that sutures the jejunal side of the mini-enterotomy and buttressing partially the stapled esophageal closure. The NG tube is pushed into the jejunum, a blue-dye test is performed and then removed. The jejunal stump is fixed to the right diaphragmatic pillar to avoid twisting and prevent hiatal herniation. The specimen is inserted in the laparoscopic bag and extracted via a suprapubic incision. When a frozen section is required on the esophageal stump, the esophagus is transected with a transverse application of a linear stapler, the whole stomach is extracted and sent for immediate examination of the esophageal side; the staple line is pierced in its middle on the guide of the NG tube pushed forward, two stay sutures including muscular and mucosal layers are placed to ease introduction of the esophageal jaw of the stapler already inserted into the jejunal stump to realize the mechanical part of the anastomosis. A running suture with a barbed 3-0 absorbable material closes both the visceral opening and completes the procedure.

# Laparoscopic Distal Gastrectomy and Indocyanine Green Fluorescence-Guided Lymphadenectomy

38

Sarah Molfino and Gian Luca Baiocchi

The clinical applications of indocyanine green (ICG) are wide-ranging, and new applications, including angiography, sentinel node-guided surgery and biliary tree visualization, are rapidly gaining widespread use [1–7]. The effectiveness of ICG fluorescence as a tracer during lymphadenectomy for gastric cancer is currently under evaluation.

In this video, we present the clinical case of 36-year-old man with a seeming early stage antral gastric adenocarcinoma, as preoperatively defined, subjected to laparoscopic subtotal gastrectomy and D2+ lymphadenectomy.

Before surgery, the patient was subjected to endoscopy in order to inject ICG near the tumor and visualize the tumor's lymphatic basin during the operation.

A 25 mg vial of ICG (Verdye, Diagnostic Green GmbH, Aschheim-Dornach, Germany) was diluted in 10 mL of sterile water, for injection the day before the operation. During the endoscopic procedures, the four quadrants around the cancer were submucosally injected with a total dose of 2 mL.

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During the operation the photodynamic eye of the laparoscopic camera clearly revealed the fluorescent nodes draining the area of the mucosal tumor making the dissection easier.

Thanks to ICG fluorescence with the light emitted from the photodynamic eye of our laparoscopic system, it is possible to clearly visualize both the individual lymph nodes and the lymphatic collectors which drain ICG (and lymph) of the specific mucosal area previously marked with ICG.

This technique could allow for a more precise and radical nodal dissection and a safer procedure respecting vascular and nerve structures. Further studies are needed to demonstrate the advantages of this technique.

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# Endoscopic Submucosal Dissection

# 39

Filippo Catalano

The endoscopic submucosal dissection (ESD) technique was firstly proposed and developed in Japan by Hosokawa for the treatment of mucosal early gastric cancer (EGC). The aim of ESD is to perform en-bloc resection of the lesion to reduce the risk of local recurrence and allow correct histological evaluation to assess curativity criteria.

In this video chapter we demonstrate the main steps in performing an ESD for EGC.

The first step of endoscopic submucosal dissection is represented by marking the normal mucosa around the lesion with at least 5 mm of free margins using a standard needle knife (Olympus Co., Tokyo, Japan) with a forced 20 W coagulation current (ICC 200 or VIO 200 ERBE, Tubingen, Germany). The next step is the lifting of the lesion with a submucosal injection; a saline solution mixed with epinephrine (0.04 mg/mL) and small amount of indigo carmine or methylene blue is used, in order to better recognize the different layers. At this point a circumferential mucosal incision is carried out outside the marking dots with a needle knife in the 60 W endo-cut mode effect 3 and then completed with an insulation-tipped (IT) knife, in the 60–80 W endo-cut mode effect 3 (ICC 200 ERBE, Tubingen, Germany). The lesion's lateral borders are now free from the rest of the tissue and the submucosal layer underneath the lesion is carefully dissected from the muscle layer with the IT knife. Hemostasis of blood vessels in the submucosal space during the procedure is achieved with the same knife or with hemostatic forceps (Coagrasper, Olympus).

Lastly the specimen is orientated on a plate and is fixed with thin needles circumferentially, on the edge of the resection to allow correct histological evaluation.

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# Correction to: Gastric Cancer: the 25-year R-Evolution

Giovanni de Manzoni and Franco Roviello

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The book was inadvertently published with an incorrect copyright year and it has been updated as 2022.

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