Vivian E. Strong
Editor

Gastric Cancer

Principles and Practice

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This book is dedicated to those who strive for improvement in the field of gastric cancer; the science, the technique and the clinical care of our patients. With deference to those who paved the way before us and with hope for the discoveries yet to come.

Preface

Gastric cancer has been declared by the World Health Organization (WHO) to be a Global Public Health Concern, with nearly 1 million new cases worldwide per year. Although the incidence is highest in Eastern parts of the world, South America and Eastern Europe; rates are also increasing in western countries such as the USA. Not only proximal gastric cancers are increasing in incidence but also distal gastric cancers in the young age group of 25–39.

In the last 15 years, our progress and understanding of this cancer have exploded. Revolutionary progress has been made in both the understanding of gastric cancer as a heterogenous disease with many subtypes, as well as in our multidisciplinary strategies to treating gastric cancer—from minimally invasive techniques to novel chemotherapeutic agents. We have a far better understanding and with improved molecular characterization, these differences are becoming more apparent and hopefully will lead to better targeted approaches to the treatment of various forms of gastric cancer.

In this volume, there is the amalgamated knowledge of the foremost experts and leaders in the field of gastric cancer from around the world. Each author is a respected and recognized authority in his or her field that has been especially handpicked for the topics presented. Currently, there is no textbook entirely devoted to the pathophysiology, management, and treatment of gastric cancer. This textbook is designed to provide a comprehensive and current overview of the important issues specific to the field of gastric cancer. Care of these patients and clinical conditions can be quite complex, and materials have been collected from the most current, evidence-based resources, providing an overview of all aspects of gastric carcinoma, from the historical perspectives and epidemiology to the surgical approaches and oncologic treatments, to the most innovative, molecular advances that will further launch our understanding of this complex disease forward.

On behalf of all the authors and myself, we sincerely hope this text will serve as a valuable and useful guide of better understanding and treatment strategies for those who are interested in providing the very best approaches to the care of our patients with gastric cancer.

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Part I

Historical Perspective and Gastric Pathophysiology

The Historical Perspective of Gastric Cancer

1

Michael A. Rogy and Marius A. Bünger

You are looking for an answer to a certain problem in the field of medicine? Doubtless, it has become common practice to sift through the relevant special literature for the most innovative, most recent findings. As a result, the community of scientists also focuses interest and ideas on trends, just like society in general.

This overriding interest in topical literature might occasionally be to the detriment of earlier concepts of theories, substituting reevaluation by accepting them as given facts. Focusing on the most recent findings is considered worth the time input; there is practically no time left for dealing with the past.

The discussion on the historical development of the treatment of gastric cancer is meant to be conducive to a deeper understanding of various strategies of treatment.

When studying older publications, names of committed physicians and scientists, fascinating past interconnections and judgments based on experience develop—in the case of the history of gastric cancer tracing back to the nineteenth century [1]. These days, historical therapeutic developments mostly span several decades only, and quite often scientists have succeeded in developing a strategy for curing the illness in question over the years.

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The historical development of the therapy of gastric cancer spans more than a century. Pioneer work has been done by great surgeons like Theodor Billroth (Fig. 1.1) in Vienna, John Jones in the USA, and an incredible number of physicians and scientists who have looked into the subject ever since.

In the autumn of 2014, studying historical connections in the field of gastric cancer therapy led to a deepened understanding of therapeutic concepts comprising a time span of more than 130 years.

Widely different measures of cancer therapy used in the course of decades have been evaluated in numerous studies. By surveying different treatment strategies over such a long stretch of time, some committed physicians/scientists may feel inspired to develop new ideas and concepts of treatment [2].

Taking a present-day view on past failures of studies can help draw vital conclusions for today's work and make for reassuring motivation.

There is an additional opportunity to be found in studying the history of various therapeutic procedures: a decisive detail may have simply been overlooked until today.

Decades of Surgery Development

The idea to perform a stomach resection because of a carcinoma of the pylorus was developed by Dr. John Jones, the first professor of surgery at King's College, and a cofounder of the New York Hospital. Jones wrote the first American textbook on

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Fig. 1.1 Theodor Billroth (1887)

surgery in 1775. Around 1800, influenced by the painful death of a friend due to a carcinoma of the pylorus, Jones performed resections of the pylorus on dogs and rabbits, however without success.

Time had not come yet for that kind of surgery in the eighteenth and early nineteenth centuries. For tackling the problems of gastric surgery, three preconditions had first to be resolved: (1) the sero-serose suture technique (Lembert 1826), (2) antiseptic wound therapy (Semmelweis 1847, Lister 1867) and (3) pain treatment during such time-consuming operations (Jackson 1841, Morton 1846).

In 1874, it was Professor Billroth who instructed his assistants Gussenbauer und Winiwarter to develop a surgery technique in dogs for prospective stomach resection in humans. Gussenbauer developed the anastomosis of both lumina with a Lembert suture line. However, out of seven dogs only two survived: two of them died after anastomotic leakage; one after contact infection; and two more from ileus.

In the course of these experiments on animals, some problems were successfully resolved: First, the assistant surgeons could demonstrate that in five out of seven dogs the suture lines were not destroyed by stomach fluid; second, that the serosa between stomach and duodenum healed neatly; third, that the ligature of the vessels along the smaller and greater curvature of the stomach did not lead to necrosis of the stomach in situ.

Gussenbauer and Winiwater also demonstrated that the two surviving dogs were able to eat and ingest food like healthy ones and, moreover, exhibited after rehabilitation no difference of behavior compared to healthy dogs. Eight months after surgery the sections of the two surviving dogs displayed in both an open anastomosis; however, one dog had a peptic ulcer at the anastomosis.

Parallel to the animal research studies, Gussenbauer and Winiwarter studied the pathology reports of patients who died from carcinoma of the pylorus between 1817 and 1873. This retrospective analysis revealed that 41.1 % (223/542) of the patients with carcinoma of the pylorus had not developed metastases but died because of tumor cachexia due to stenosis of the pylorus.

Another fact of considerable practical dimension was revealed by Gussenbauer. He detected that in 32 % of patients (172/542) the tumor was not fixed, but mobile. These results were to prove that a number of patients could be cured by the resection of the tumorous pyloric/antrum region.

Summarizing the results of the animal studies and the retrospective clinical investigations, Gussenbauer followed that "… for the treatment of stomach cancer, which is located usually at the pylorus region and leads due to local stenosis and its consequences not seldom to death, partial stomach resection should be taken into account" [1].

In 1879, Billroth reported at a surgeons' meeting that after successful treatment of an incarcerated femoral hernia with over-suturing the small bowel as well as the successful over-suturing of the stomach wall after a penetration accident time had come for surgeons to go about performing a partial stomach resection and not to fear

that stomach fluids would prevent sanatio per primam. Two contemporaries of Billroth's tried to perform stomach resections: surgeon Péan on April 9, 1879, in Paris; Rydygier in Chelmno, Poland, on November 16, 1880. Both of them failed.

Billroth was to wait for another 5 years before the right patient for a pylorus resection entered General Hospital, AKH, in Vienna. The difficulties in finding the right patients were also due to the fact that X-ray was not yet available for diagnosing such lesions. Diagnoses had to be done by a thorough clinical history and investigation of a palpable tumor.

On January 25, 1881, a 43-year-old Viennese, Therese Heller, was sent to Billroth's clinic at AKH, General Hospital. She had been suffering from typical symptoms of a pylorus stenosis for 3.5 months. Clinical investigation showed that she had on the right side of the umbilicus a fist-sized tumor that was still mobile. Although the patient was very weak, Billroth decided nonetheless to perform a pylorus resection, an operation which had been painstakingly planned by him before.

The Billroth I operation (Fig. 1.2) in chloroform anesthesia took 1.5 h. The next morning the patient only felt a little pain in the stomach region, the heart rate was 110, and she was running a temperature of 39 °C late evening. There was no change during the following 3 days. On day 4 after surgery the patient began to eat some mushy food, which agreed with her.

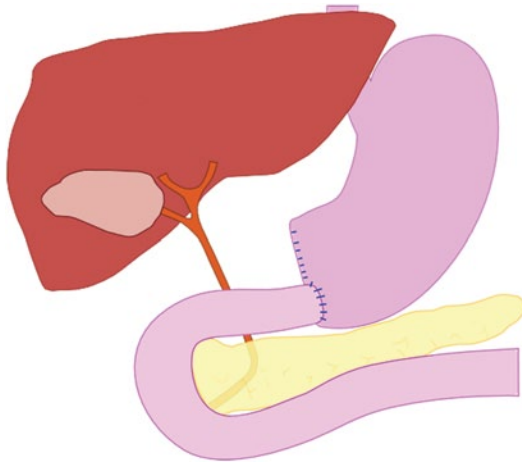

Fig. 1.2 Billroth I-gastric resection

The histology report showed a partial stomach with a length of the greater curvature of 14.5 cm and a diameter of the lesser curvature of 10 cm. There was also a 2-cm margin of healthy duodenum on the stomach. There were two tumor-infiltrated lymph nodes on the greater curvature. Microscopically, the tumor was a gelatinous carcinoma, infiltrating the subperitoneal layer.

On day 6 after the operation the wound dressing was changed for the first time. The wound healing was per primam and some sutures were removed. The remaining sutures were removed the next day. Miss Therese Heller started to eat and gained energy over the following week. She wished to be discharged from hospital when she was able to eat different meat dishes with appetite on postoperative day 22. During the following weeks her sacral decubitus was healing well.

Until March 3 the patient was under regular control by her general practitioner. She was continuously improving and ate whatever she felt like. However, by end of April, Therese Heller suffered a relapse, and quite soon it was obvious that she developed a recurrence of the cancer. She died on May 23, 1881, in Billroth's clinic at the General Hospital of Vienna (Fig. 1.3).

At a surgeons' meeting in Vienna on February 25, 1881, Billroth reported about his patient Therese Heller and the first gastric resection. In this lecture, Billroth summarized the following facts:

1. The resection of the antrum and further parts of the stomach has no influence on the digestion of the patient.
2. The ingestion of the suture material at the anastomosis is not a problem, had so far not occurred in this patient and had not been a problem for another patient on whom he performed a closure of a stomach fistula 3 years before.
3. Billroth expected a somewhat narrowing of the anastomosis; however, without any clinical consequences for the patient since he never experienced such problem in patients with small bowel resection.

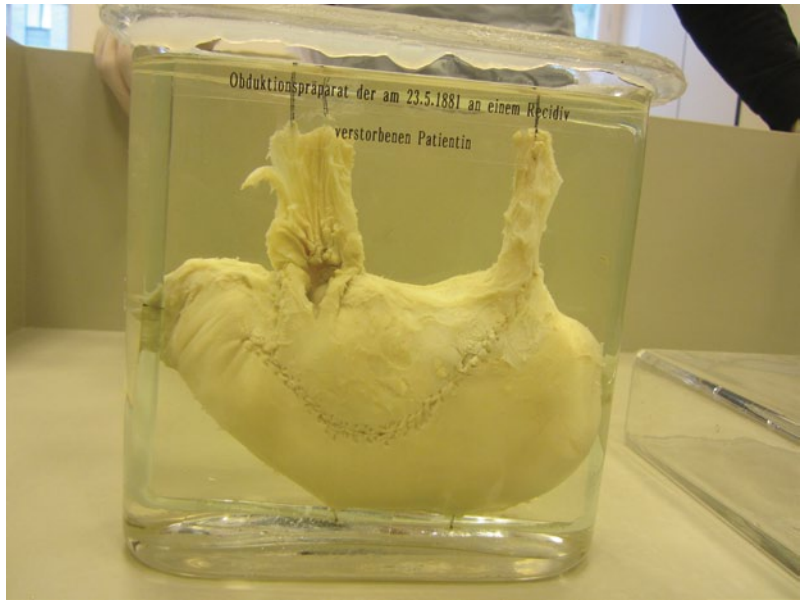

Fig. 1.3 "Post mortem of stomach of the patient with the first successful gastric resection by Billroth on January 25, 1881, who died on May 23, 1881, suffering from a relapse." Museum for medical history in Vienna, Währinger Straße 25, 1090 Wien

4. A recurrence of the carcinoma in the patient, Therese Heller, is to be expected since the adhesions he saw during the operation might come from tumor cells.

Billroth closed his lecture in saying: "At this stage we should be content that it is possible to perform a gastric resection with success. I just can assure you that Mrs. Therese Heller has been feeling much better since the first postoperative day; she has not been in pain and has had no vomiting attacks any more."

Further Resection Methods

Consecutively, Billroth developed a second resection method in 1885. Duodenum and stomach were closed blind after pylorus resection and a new connection between the stomach rest and jejunum was created. By doing this, he used anterior gastro-enterostomy, but understood carrying out Billroth II operation (Fig. 1.4) as a kind of stopgap operation [3], the reason being the passage irritations (circulus vitiosus) that occurred during the anterior/front gastro-duodenostomy.

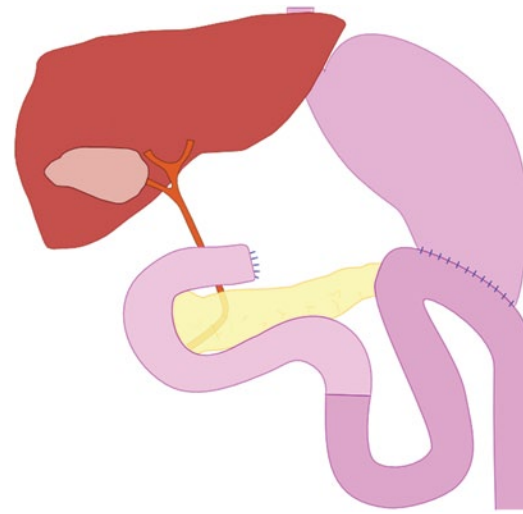

Fig. 1.4 Billroth II-gastric resection

Kocher demanded that after the excision of the gastric carcinoma the stomach had to be closed at all events, followed by a gastro-enterostomy. He blind stitched the stomach and implanted the duodenum posterior into the stomach wall. He therefore held the view that the kind of

complications occasionally observed concerning gastro-enterostomy (Billroth, method II) could be safely avoided and satisfactory results could be achieved. Nonetheless, both his method and Billroth's method I shared the same disadvantage of being only performable if the suture line of duodenum and stomach rest was tension free [4].

After this first successful resection of part of the stomach, Billroth I method, it was Connor who tried first in Cincinnati to treat a 50-year-old woman's extensive gastric carcinoma by a total stomach extirpation in 1883. It was worldwide the first ever gastrectomy performed on a human being. Unfortunately, the patient died while being operated upon [5].

In 1897, Swiss surgeon Schlatter had a brilliant idea: the first ever esophago-enterostomy after gastrectomy. The beginning of numerous consecutive variants of surgeries following the example of gastrectomy. Schlatter pulled a small bowel loop antecolically towards the lumen of the esophagus and connected them—after a longitudinal section of about 1.5 cm on the small intestine—by running circular sutures.

His patient gained 8.5 kg within 9 months but died 14 months after the operation on a recurrence [6]. Despite the fact that a tiny part of the stomach was detected during section, this case provided evidence that a human being can live without a stomach.

In 1898, a year after Schlatter's first total resection, MacDonald successfully carried out a gastrectomy on a 38-year-old patient who was able to leave hospital on day 13 after complication-free progress. The patient's survival span is not known. The same year Brigham was third in line to successfully perform a gastrectomy. He managed to create an anastomosis between esophagus and duodenum on a 66-year-old woman. She survived for 2 more years.

In principle, gastric cancer surgery cannot be understood as a standard method in its first phase when the focus was still on researching and ongoing development of methods. More generally, it can be stated that gastro-enterostomy and pylorus resection were given approximately the same attention and priority over gastro-enterostomy, in particular during the early period before 1900.

The innumerous variants of gastro-enterostomy—not all of them can be mentioned here—speak of the importance attached to this operation at the turn of the nineteenth century. This is also due to the fact that the majority of patients did not become symptomatic before an advanced stage and only then consulted a doctor. There was general awareness of the fact that excision of the carcinoma, namely resection methods as, e.g., pylorus resection, constituted the only prospect of cure [7].

Then and there, gastrectomy was playing a rather subordinate role. Although it was successfully carried out by known surgeons, it was not popular with the broad mass of surgeons at the beginning of the twentieth century because of the inherent technical difficulties. Occasionally, voices were raised that there was in all probability no future in stomach extirpation [8].

Finney and Rienhoff counted 122 cases from the years 1884 to 1929 of stomach extirpation because of gastric carcinoma mentioned in the literature. Only 67 cases were considered genuine "total gastrectomy," namely those where a total resection of the stomach including cardia and pylorus could be assumed.

Finney's and Rienhoff's data compilation shows that in keeping a part of the stomach—whatever size—reduced the hazards of operation drastically. Direct comparison with the group of total resections yielded a 28.8 % decrease of mortality rate [9].

Causes of Death

When interpreting causes of death, anesthesia must be taken into account. Anesthesia was then at a fairly young age of about 50—not yet fully mature—and therefore certainly the cause of many surgical incidents. Moreover, although the term "asepsis" had been known since 1847, antiseptic measures were not as strict as today. It was a general practice to operate with bare hands on patients—at least before 1890, when Halsted introduced rubber gloves. Face mask and surgical coat became even later part of surgeons' work wear.

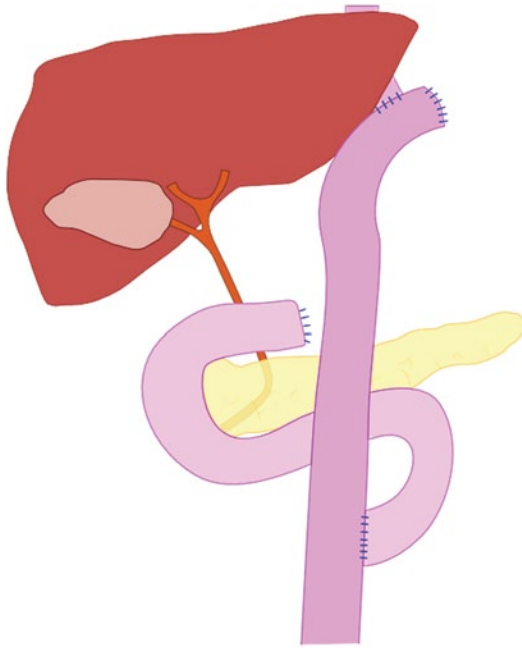

Fig. 1.5 Y-Roux reconstruction after gastrectomy, developed in 1907

Despite relative inexperience in matters of hygiene and anesthesia, peritonitis and shock took first places as causes of death. These two were caused, among other things, by technical deficiencies. Most surgeons used the running two-row suture for anastomoses, but suture insufficiency was extremely problematic to handle [10].

Another frequent cause of death was pneumonia, often in combination with pulmonary gangrene [11]. The longer an operation took, the greater was the hazard of pneumonia.

The great number of publications on gastrectomy and its reconstruction potential in the 1940s and 1950s of the past century provide evidence of how intensively the topic was being dealt with then and there. Roux introduced as early as 1907 the end-to-side anastomosis of the afferent loop (Fig. 1.5). After occluding the duodenal stump, he skeletonized a jejunal segment (about 20–30 cm aboral of the flexura duodenojejunalis) and cut the intestinal tube through. Then the aboral small intestine was taken up retrocolically to the esophagus and anastomosed with the latter. Safeguarding the suture was achieved by a simple segmental jejuniplication. The small intestinal tube was closed by means of terminal–lateral anastomosis below the transverse colon [12].

In 1952, Hunt combined Roux's loop building with pouch reconstruction, an attempt to prevent reflux into the esophagus. After gastric resection he occluded the duodenal stump blind and severed the jejunum approximately 30–35 cm below the Treitzsch ligament. Then he pushed the distal branch antecolically up towards the esophagus and formed from its end a kind of loop that was anastomosed at a length of approximately 15 cm side-to-side. This procedure yielded a kind of tube that was connected end-to-side with the esophagus. Finally, the proximal jejunum was anastomosed laterally to the distal jejunum [13].

In 1952, Longmire seized upon Seo's idea of interposition of a short segment of the small intestine between esophagus and duodenal stump. He isolated a segment of approximately 10–15 cm from the upper jejunum, preserving its nutritive vessels, anastomosed the two jejunal lumina and positioned the jejunal segment between esophagus and duodenum. All three anastomoses were end-to-end connections [14].

On the basis of a collective statistic of different specialist surgeons, Pack and McNeer highlighted the frequency distribution of surgical procedures concerning passage reconstruction after gastrectomy. From 1884 till 1942 esophago—jejunostomy was continually gaining ground as the surgical method of choice: between 1884 and 1920 it was at least equivalent to the esophago–duodenostomy; between 1921 and 1930 with a rate of 64.9 % it was deployed more than double as much as the other; from 1931 till 1942 esophago–jejunostomy reached 95.1 %—and was thus the absolute lead [15].

Steingräber compiled from 36 authors' reports 219 fatalities after gastrectomy between 1927 and 1952 [16]. During this period, peritonitis ranked first as the cause of death. Frequently technical deficiencies were to blame for this, in particular, caused by insufficiency of esophageal anastomosis [17].

Acceptance concerning gastrectomy was continually gaining importance after 1940, beating subtotal stomach resection to second place as the

curative resection method of choice. At that time, preference was given to extended gastrectomy, accompanied by additional resections of the omentum as well as distal pancreas and spleen.

Out of a total of 287 patients, treated at the Memorial Sloan Kettering Center, New York, 263, i.e., 91.6% could be operated on; 112 of these underwent curative resection (39%). Between 1951 and 1954 the 5-year survival rate of the patients who were curatively resected was 23.2% for all patients and 26.8% for the 40 patients who survived surgery. In comparison, the 5-year survival rate of patients treated between 1931 and 1950 was 21.6%—not much of a difference—although expanded gastrectomy was deployed more frequently in comparison between 1951 and 1954 [18].

Subtotal Gastric Resection or Gastrectomy?—Indications

Holle and Heinrich published an attempt at establishing criteria for an indication of whether to choose partial or total resection in 1960 [19]. So as to facilitate decisions for the appropriate measures to be taken, Holle and Heinrich classified cases as different groups (A, B, C):

- A-case: tumors that were confined to the stomach and had not yet developed visible or palpable metastases in the regional lymph nodes belonged to this group. According to the authors, partial resection was in general in line for such cases if the demand for radical removal could be fulfilled.
- B-case: Bigger, still movable tumors confined to the stomach but with visible metastases in one or two lymph drainage areas were subsumed in this group. Holle and Heinrich recommended for this group total resection followed by small intestine interposition according to Longmire.
- C-case: This group comprises advanced cases. The tumor had transgressed the stomach borders in at least one direction and developed regional metastases, or even distant metastases. Here, the sole purpose of surgery was to provide palliative measures for pain relief.

The authors held the opinion that in the wake of decreasing surgery fatalities in connection with total gastrectomy (then 10%; in some places as low as 3–4%) the administration of total gastrectomy for the B-cases was justifiable. Surgery mortality did not differ much from partial resection, which was sufficient reason to prefer total gastrectomy. After all, the principle of radical surgery had been long around for cancers of other organs. Primary mortality rates of up to 50% connected to total gastrectomy had so far been an indicator against taking radical measures.

The Role of Lymph Node Dissection

In the early 1940s, Coller, Kay, and McIntyre published a study of all regional lymph nodes—a veritable eye-opener for many surgeons [20]. Forty out of 53 cases of gastric carcinoma showed positive lymph node involvement. According to their findings, the most frequently involved lymph node groups were the "inferior gastric-subpyloric" and the "superior-gastric" lymph nodes.

There was neither a relationship between the duration of symptoms and the occurrence of lymph node metastases, nor a relationship between tumor size and the existence of lymph node metastases detectable. However, what they were able to point out was that the probability of metastasis in the regional lymph nodes increased with the depth of tumor cell infiltration in the stomach wall. Metastasis was provable even for the majority of cases where regional lymph nodes were either not palpable or, if palpable, considered nonsuspect by surgeons. This explains why the authors recommended including the 4 lymph node zones into the resection—irrespective of whether lymph nodes were palpable or not—for the sake of better chances of cure.

Between November 1950 and January 1953, Sunderland et al. also carried out a study on lymph node metastasis connected to gastric cancer—similar to the one conducted by Coller et al. 10 years before [20]. Based on 41 preparations investigated, the authors arrived at the following conclusions:

- Lymph node metastasis had occurred in 85% of the cases
- Tumors of the proximal third of the stomach metastasized preferentially in the superior, paracardial and pancreatico-lienal lymph node groups; tumors of the distal third showed frequently metastasis in the superior, subpyloric and inferior lymph node groups; tumors of the medium third, as well as such that involved the whole, metastasized at similar rates in all regional lymph node groups.
- In case the gastric carcinoma was located in the proximal or medium third, more lymph node metastases were found; the highest quantity of lymph node metastases were diagnosable when the tumor had involved the whole stomach.
- Depth of tumor (cell) infiltration appeared to have a crucial influence on the amount of lymph node metastases.

Remine and Priestley investigated the relation between localization of infiltrated lymph nodes and reported their results in 1953.

What struck them was the fact that with the group of 5-year survivors only 6% had subpyloric lymph node metastases. While the group of earlier fatalities showed 71% subpyloric lymph node metastases.

Laurén—Classification of Gastric Carcinoma

Classification according to Laurén differentiates on the basis of morphological criteria between two types of gastric carcinoma:

- Intestinal type, which is sharply demarcated against the environs. This type creates glands of cylindrical epithelium (cells) that resemble intestinal epithelium and produce mucus.
- Diffuse type, de-differentiated adenocarcinoma with considerable cell dissociation or else " signet ring cell" carcinoma, which are but diffusely demarcated against the environs [21].

"Gastrectomy totale de principe"

French surgeons Lefèvre and Lortat-Jacob demanded in 1950 "gastrectomie totale de principe," based on the principle that —whatever gastric carcinoma was concerned—gastrectomy was to be carried out as principle gastrectomy. This demand contradicted the view held by many surgeons that "gastrectomie totale de nécessité" should only be performed in case of total involvement of the stomach. They had many followers but also met with opponents [22]. Lefèvre and Lortat-Jacob argued that their demand was corroborated by the respective literature that certified lower rates of fatalities after gastrectomy [23, 24]. Their fundamental idea was one of decreasing the number of local recurrences by heightened radicalness—and thus achieve better survival rates [25].

"Gastrectomy de nécessité"

Proponents of gastrectomy "de nécessité" held the opinion that there existed no such procedure like a "standard procedure" because gastric carcinoma as such did not exist either. In their view, there were various different pathological–histological and clinical forms of gastric carcinoma that necessitated individualized, stage-oriented treatment [26, 27].

Next to preoperative staging, knowledge of the histological-morphology of the gastric carcinoma (ever since Laurén introduced histological tumor classification) was playing an increasingly significant role, when it came to choosing the appropriate method of therapy.

Knowledge of the tumor type, gathered from different observations on tumor sectates and the expansion of the tumor depending on its type—was to determine the method of therapy. Whereas the intestinal type and the diffuse type, that was restricted to mucosa and sub-mucosa, expanded only a few millimeter beyond the tumor limits macroscopically discernible, the diffuse, advanced carcinoma behaved differently: although the tumor wall showed macroscopically no pathological findings, tumor cell clusters were

histologically discernible even several centimeters away from the macroscopic tumor border [28].

Therefore, oral and aboral safety zones were devised to do justice to the different histological-morphological diagnoses according to Laurén. Although the primary tumor was resected, keeping to the necessary safety zone, lymph nodes without pathological findings were not resected. It was self-understood that for tumors of the upper third of the stomach, as well as of diffuse type tumors of all sections of the stomach, gastrectomy was the method of choice in order to keep to the peri-tumoral safety zones [29].

Gastrectomy "de principe" was only opposed in cases of gastric carcinoma of the distal third and certain carcinoma of the medial third, of the intestinal type [30]. Main arguments against gastrectomy "de principe" were higher surgery fatality and a falling-off quality of life. Better life quality could be achieved by leaving the rest of the stomach [31].

What arises from the compilation of studies is the fact that even today gastrectomy is accompanied by complication rates about 10–15 % higher in comparison to subtotal stomach resection.

Indication Concerning Gastrectomy, Respectively, Subtotal Stomach Resection

According to guidelines for multi-modal therapy of gastric carcinoma, decreed in 1995 by three task groups of the Deutsche Krebsgesellschaft (German Cancer Association), therapy by surgery necessitates keeping an adequate safety zone of 5 cm, respectively, 8 cm in situ.

Decision making for either gastrectomy or else subtotal resection depends on tumor localization, histological–morphological type and individual assessment of risk. As a rule, the diffuse type requires gastrectomy. As long as an oral safety zone of 5 cm can be warranted, subtotal resection and gastrectomy for carcinoma of the intestinal type in the distal and medial thirds of the stomach appear to be of the same value [32].

Quality of Life After Stomach Resection

Surgery fatality, morbidity, and 5-year survival rates are the decisive factors of prognosis after surgical treatment of gastric cancer. As technical problems have been solved by and large in recent years and fatality and morbidity, also with gastrectomy, have been going down to values that can hardly be changed, the focus is now on yet another criterion of judgment when looking for an appropriate method of treatment: postoperative quality of life. Surgeons have to aim at making the potentially short span of life remaining as bearable as possible for the patient. So far, there is no standardized definition of "quality of life" available, since the term embraces ever so many aspects to be considered when trying out different methods of measurement [33].

Subtotal Gastric Resection Versus Gastrectomy

Meanwhile, in the case of curative resection, subtotal stomach resection and gastrectomy—allowing for the principles of radicalism—do not show prognostic differences any more [34]; more attention is being paid to quality of life as an indicator of successful surgery. Hereby, subtotal gastric resection is generally understood as the more physiological procedure, supported by postoperative gastrectomy diagnostic findings such as the Dumping Syndrome, postprandial flatulence or pain, and hungry [35]. More recent studies have tried to objectify these ailments and compare quality of life after subtotal resection and gastrectomy according to different scores [36].

Systematic Lymphadenectomy

Although the role of lymph node dissection had already been realized in the 1940s and 1950s, results were not convincing enough to concede standing to a more radical procedure for surgery treatment of gastric carcinoma. Recognition was emerging gradually owing to Japanese study

data. Japanese surgeons practiced for more than two decades systematic extended lymph node dissection (SELD) at gastric carcinoma surgery. Their results underscored the significance of systematic lymphadenectomy for obtaining increased 5-year survival rates [37].

While investigating lymph nodes, the Japanese drew on the cataloging of different lymph nodes described by the Japanese Research Society for Gastric Cancer (1981). Thus, each lymph node is given a number (1–16), gets attributed to an anatomical region, and is then, according to its distance from the stomach, subsumed together with other lymph nodes in a group. There are altogether three groups (compartments).

Compartment I (numbers 1–6) comprises lymph nodes that lie most densely on the stomach wall. Compartment II comprises lymph node numbers 7–11; compartment III, numbers 12–16, comprises lymph nodes further away from the stomach.

1.	Right para-cardial	9.	Truncus coeliacus
2.	Left para-cardial	10.	Spleen hilus
3.	Smaller curvature	11.	A. lienalis
4.	Bigger curvature	12.	Lig. Hepatoduodenale
5.	Supra-pyloric	13.	Retro-pancreatic
6.	Subpyloric	14.	Mesenterial radix
7.	A. gastrica sinistra	15.	A. colica media
8.	A. hepatica communis	16.	Aorta adominalis

In the wake of increasingly applied SELD, a discussion of how to define this procedure became a crucial issue. So far it had been mostly left to the surgeon to decide how many lymph nodes had to be removed. He oriented himself initially mostly on a medium value of 30 lymph nodes—this medium value was established by Soga and collaborators in the framework of investigating 530 gastrectomies [38].

According to their findings, a lymphadenectomy on gastric carcinoma could be considered sufficient if a minimum of 28 lymph nodes were to be removed. Additionally, they stated that splenectomy alone in addition to lymphadenectomy did not result in remarkable improvement in the sense of radicalness. In the course of a so-called simple gastrectomy an average of 26.2 ± 1.9 lymph nodes were removed. Gastrectomy together with splenectomy could increase the amount only to 29.3 ± 2.3.

The declared aim of extended lymphadenectomy was the enhancement of R0- resections as well as achieving a lymphogene safety distance of resected involved lymph nodes from nonresected, noninvolved lymph nodes of Compartment III. Hence, an improvement of prognosis was to be expected in a single subgroup only, namely in the one that showed exclusively lymph involvement of Compartment I. This expectation was actually corroborated by prospective studies [39].

However, data gathered by a Dutch and British Multicenter study did not bear out any kind of advantage for survival after SELD. Both studies undertook comparisons of 5-year survival rates after D1, respectively, D2—lymph node dissections. The 5-year survival rates for both groups were almost identical. The Dutch study shows a 5-year survival rate of 45 % for the D1 group in comparison to 47 % for the D2 group; the British study shows 35 % for the D1 group, and 33 % for the D2 group [40].

Closely related to systematical lymphadenectomy is the issue of splenectomy "en principe" in connection with gastric carcinoma. It was recommended already in the early 1970s under the aspect of radicalness [41], but has been increasingly criticized in the course of a more differentiated position of indication since the 1980s [42].

The spleen is rarely tumorous, but an infiltration of lymph nodes in the hilum area was observed in up to 40 % of gastric carcinoma [43]. Therefore the method of en-bloc resection of the spleen together with the stomach was widely used in the curative surgery of stomach cancer in the 1970s. In the case of carcinoma of the upper third of the stomach this procedure was evidence-supported by lymphogram data [44] that proved lymph drainage from the left upper stomach region via spleen hilum and along A. lienalis towards truncus coeliacus.

More recent studies described the incidence of spleen–hilum lymph node metastases of carcinoma of the proximal third of the stomach as up to 26.3 %; for antrum carcinoma as 0–7 % [45].

Koga provides results (ranging from 1960 to 1978) after gastrectomy together with splenectomy, respectively, pancreatic-splenectomy, and gastrectomy with preservation of the spleen. Hence, 5-year survival rates for stages I and II amounted to 86 % in the group of non-splenectomized and was therefore higher than in the group of splenectomized (65 %). Even though these results are statistically not significant, they suggest that a preservation of the spleen in stages I and II appears to make sense [46].

As for survival span, no statistically significant difference between preservation of spleen and splenectomy could be found by Brady et al. or Adachi et al. [47]. For a definite assignation of the place of splenectomy for the surgical therapy of gastric carcinoma further prospective randomized studies have to be made. So far splenectomy is indicated in cases of T2–T4 tumors of the medial and proximal thirds of the stomach, also for direct infiltration of the spleen, and advanced T3/4 tumors [48].

Resigning to the fact that prognostic gain for patients can only be won by local freedom from tumor (R0- resection), prognosis improvement by extended gastrectomy, including co-resection of adjacent organs, has met with occasional attention over the past 20 years. Except for Japan, publications on the topic are few and far between; their results will be mentioned in the following.

T4 tumors cannot be generally considered as inoperable. By means of several results from studies it can be shown that it is not the T-category, but involvement of lymph nodes, the existence of incurable factors like peritoneal carcinosis and distant metastases that influence prognoses most significantly [49]. Therefore, patients with an advanced T4-tumor without involvement of lymph nodes have a better prognosis than patients with involvement of lymph nodes [50].

In fact, total resection of the tumor is recognized as the only potential curative therapy of gastric carcinoma, but despite rising rates of tumor resection [51] it is the sad truth that the development of local recurrences in 10–30 % of cases keeps the percentage of 5-year survival down to a depressing 20–30 %. This figure gives rise to testing new complementary methods of treatment [52], two of them being chemotherapy and radiation therapy.

Systemic Adjuvant Chemotherapy of Gastric Carcinoma

First Tests with Thiotepa, Respectively, 5-Fluorodeoxyuridin

In the 1960s and the 1970s, members of the study group The Veterans' Administration and the University Oncology Group pioneered testing chemotherapeutics like Thiotepa and 5-Fluorodeoxyuridin after gastric resections—without success. Not a single study showed any significant difference in survival rates between patients treated with chemotherapeutica and the control group [53]. On the contrary, the toxicity of the substances worsened survival chances. Surgery mortality after administering Thiotepa to the target group doubled (20 %) in comparison with the control group and was not relevantly improved by reducing the doses [54].

In the 1960s and 1970s, 5-fluoroutacil was the most intensively tested substance for treating gastric carcinoma [55]. By 1974 Comis and Carter compiled data of 450 patients who had been treated with 5-fluorourcil. However, they had been treated with different schemata, of which Ansfield's and Curreri's was the most frequently used. They recommended a dose rate of 15 mg/kg/dx5, followed by half this rate every other day until the appearance of symptoms caused by the toxicity of the substance [55].

According to Carter and Comis, the wide spread of response to treatment could be explained by differences in selecting patients and intensity of therapy. Although activity of 5-fluorouracil could be proved in the treatment of advanced gastro-intestinal tumors, it was of no use as a means of monotherapy in cases of curative resections. The second most frequently used substance was mitomycin C, isolated from populations of *Streptomyces caespitosus* [55, 56].

Polychemotherapy 5-FU/MeCCNU

In the early 1970s results from a number of gastro-intestinal tumor gave rise to the assumption that a combination of 5-fluorouracil and chloroethynitrosourea-methyl-CCNU could be successful also for treating advanced gastric carcinoma [57]. A number of research groups tested these substances as adjuvant therapy measure, but only the findings of the "Gastrointestinal Tumor Study Group" (GITSG) showed a slight improvement of survival rate by approx 15 % with patients who had been treated with these chemotherapeutics [58]. This result was not corroborated by any of the other groups [59]. As the long-term toxicity of methyl–CCNU and its secondary damage like the myelodysplasia syndrome were known; the substance was abandoned soon.

In the late 1970s a number of other substances in combination with fluorouracil underwent testing. The remission rate of 20 % when fluorouracil was used as monotherapy was heightened when used in combination with mitomycin, carmustin, and doxorubicin.

FAM

A significant improvement of results achieved by the combination of fluorouracil, adriamycin, and mitomycin (FAM) was first reported by MacDonald and collaborators in 1979. Response to treatment in their Phase II-study amounted to 50 %; median survival span for all patients treated was 5.5 months; for patients with partial remission 13.5 months. Total remission was not archived; median duration of remission was 9.5 months [60].

Individual follow-ups were investigated for up to 36 months. Dieback curves of patients with chemotherapy resistance took an unfavorable course. In the early 1980s, FAM was ranked as standard therapy for treating advances gastric carcinoma—even though success failed to appear.

FAM modifications did not yield better treatment outcomes either [61]. A series of tests was undertaken in this respect:

- Augmentation of 5-fluorouracil and adriamycin dose rates
- Replacement of 5-fluorouracil by Ftorfur; replacement of mitomycin C by cyclophosamid or BCNU
- Adding a fourth substance (e.g., methyl-CCNU or BCNU) to the original scheme.

Remission rates varied between 9 and 65 % and were comparable to remission rates of 11–60 % after using FAM [61]. In conclusion, none of the modifications mentioned yielded advantages vis-à-vis the original composite.

In the 1980s new chemotherapy combinations were developed that appeared to be superior to older regimen like FAM. Promising results were attained by FAMTX (5-FU, adriamycin, methotrexate). EAP (etoposid, adriamycin, cisplatin) and cisplatin/5-FU combinations [62].

Cisplatin Combinations

In the early 1980s the attainment of remission rates of more than 20 % when using cisplatin as monotherapy [61], plus a 6 % proportion of complete remission [63] gave rise to hope for an improvement of results by introducing Cisplatin instead of Mitomycin to the FAM regime. Six studies of the 1980s show rates of response to FAP of 29 and 55 %, and a median survival span of 4–12 months [64]. Results were comparable to those gathered from FAM studies.

FAMTX

Additionally, research was carried out on the implementation of methotrexate as a fluorouracil—modulating substance in a FAMTX protocol. The authors first claimed a response rate of 63 %; later studies showed 41 %. Klein and collaborators report a complete remission rate of 6 % [65]. Owing to its considerable toxicity, methotrexate could only be administered to patients who were in good general condition.

EAP

In the early 1980s, a combination of etopsid, doxorubicin and cisplatin (EAP) proved to be active in the treatment of local, advanced gastric carcinoma [66]. A number of studies carried out over the following years were to bear out this activity [67]. Complete remission rate was an average of 9 % [67]. Nonetheless, the enormous, life-threatening toxicity of this form of therapy was repeatedly described [68]. Therefore, in direct comparison with FAMTX, FAMTX was given preference in case of similar response to treatment [69].

In 1993, Hermans and collaborators confirmed by means of data gathered by a meta-analysis the prevailing view that adjuvant chemotherapy would be of no advantage in cases of curative resected gastric carcinoma [70].

Preoperative Chemotherapy of Gastric Carcinoma

By the middle of the 1980s successful treatment with various cytostatic drug regimens for palliative reasons was established. Subsequently, the idea of neo-adjuvant chemotherapy was put into practice with the aim to minimize preoperatively partially resectable or non-resectable gastric carcinoma tumor stage T3/4N1 ("down staging"), step up curative resection rates and improve long-term prognosis of surgical therapy [71]. Moreover, it was hoped that patients would be able to tolerate the toxicity of substances applied better before surgery.

Theoretical Bases of Neo-adjuvant Chemotherapy

Findings from diverse experimental investigations indicated that the surgical trauma created a stimulus for the remaining tumor cells, a result that strengthened belief in the effectiveness of neo-adjuvant chemotherapy [72]. This became manifest in the increase of proliferation rate, reduction of tumor doubling time, and a rapid growth of size and amount of distant metastases.

Experimental studies showed that preoperative chemotherapy, applied for tumor reduction, averted proliferation stimulus and prolonged survival time [73].

There was still another argument that recommended preoperative chemotherapy, namely the study-based fact that blood supply postoperatively was to the detriment of adjuvant chemotherapy measures. Concentrations that reached tumor remains were insufficient [74].

For the majority of cases, neo-adjuvant chemotherapy can meet the claim that by reducing the tumor mass preconditions are created that allow for complete resection of tumors that have also been diagnosed by laparoscopy as non-resectable. It can be done for 60–90 % of gastric carcinoma patients after chemotherapeutical treatment. However, complete histological–pathological remission has seldom been observed.

Intra-peritoneal Adjuvant Chemotherapy

Therapeutic failure after R0-resections that were made possible by neo-adjuvant or primary preoperative chemotherapy manifested itself primarily in peritoneal recurrences [75]. In 1987 Markman based the description of intraperitoneal chemotherapy for malign diseases of the gastrointestinal tract on this knowledge [76]. Also, Sugarbaker discussed the theoretical advantages of an instantly implemented postoperative intraperitoneal chemotherapy in 1989 [77].

Preclinical tests support this thought. Archer and Gray could show on the example of a rat model that peritoneal as well as liver metastases responded to intraperitoneal chemotherapy [78]. Sugarbaker compared in a study the results of intraperitoneal vs. intravenous chemotherapy for colon carcinoma. In contrast to intravenous therapy, intraperitoneal chemotherapy effectuated a considerable decrease of peritoneal metastases. These considerations and observations led to studies about intraperitoneal chemotherapy for patients with gastric carcinoma. Substances

like mitomycin C, 5-FU, floxuridin, and cisplatin were implemented. Initial results were not too encouraging, though [79].

Takahashi and collaborators saw the supporting medium as the potential cause for the failure of intraperitoneal forms of therapy. They assumed that water soluble supporting media, so far physiological salt solution, transmigrated too quickly through the serosa of the peritoneum and thus prevented deployment and impact of cytostatic drugs [80]. Taking this into account, they developed a novel method of treatment, the conjugation of mitomycin C on activated carbon particles (MMC—CH). The activated carbon particles were to warrant transport of the cytostatic drug straight to the place of reception in the peritoneum, the lymphatic texture, and thus guarantee retarded release of the substance mitomycin C.

The following two studies can be understood as giving direction in the treatment of peritoneal carcinosis of local, advanced gastric carcinoma.

In a prospective, randomized study between 1987 and 1992 the method (MMC-CH) was tested with a view to prevention of intraperitoneal recurrences and improvement of survival time [81].

One hundred and thirteen patients, who had undergone radical resection because of gastric carcinoma and, additionally, showed a definite serosal infiltration of the tumor, were accepted for a study and randomly divided into the MMC-CH group and the control group. Two- and three-year survival rates for the MMC-CH group were 42 and 38%; 28 and 28% for the control group. There was also a statistically significant difference concerning the 2- and 3-year survival rate ($p<0.05$).

When taking into account only the patients with macroscopic peritoneal carcinosis, survival times did not show any differences between the two groups. Statistically significant differences were noticeable when comparing 2- and 3-year survival rates of curatively resected patients: 66 and 66% vs. 35 and 20% ($p<0.01$). These findings show that intraperitoneal chemotherapy with mitomycin C ligated carbon particles appears to be an effective means for fighting peritoneal recurrences of "curatively" resected advanced gastric carcinoma with serosal infiltration. It does not prolong survival times of palliative resected patients with macroscopically visible peritoneal involvement.

Hamazoe et al. also reported on successful treatment of peritoneal recurrences. They applied a technique of hyperthermal peritoneal perfusion on 42 out of 82 patients with gastric carcinoma and evident serosa infiltration. Mitomycin C was applied in this way immediately after resection. Forty patients with radical resection only served as control group. Survival rate for patients who had received intraperitoneal chemotherapy was 64.3%; for the control group it was 52.5%—this difference was statistically not significant [82].

Intraoperative Radiation Therapy (IORT)

Intraoperative radiation therapy of gastric carcinoma was first introduced by Japanese Abe in the 1980s. With the help of IORT he tried to reach regions that were difficult to reach by surgery, such lymph node metastases along the A. gastrica sinistra, the A. hepatica communis. He ascribed the rather poor surgical successes mainly to lymph nodes that had not been resected and the fact that microscopic lesions were not detected.

Thanks to his new method it became possible to radiate the requested structures directly with the help of an attachable conus without damaging the adjacent organs, as was the case with extreme radiation [83].

For Abe, indications for using IORT were the following cases of gastric carcinoma:

- No liver—or peritoneal metastases
- Preceding surgical extirpation of primary tumor
- Lymph node metastases confined to lymph node group II.

In direct juxtaposition of results of exclusively surgically treated patients and those who had been treated with a combination of surgery and IORT results of 1987 [84] showed an improvement of 5-year survival rates due to additionally applied IORT in the stages II, III, and IV, but which were not statistically significant. These results were confirmed by a follow-up study [85].

In a publication from 1987, Abe assigned the belonging to the individual stages to macroscopic criteria, but next time round, assignment to stages was based on histological–pathological criteria. To put it differently, applying IORT was advantageous in terms of survival chances for patients with tumors that had infiltrated the serosa and also for patients with lymph node metastases of lymph node groups 2 and 3 (according to the General Rules for Gastric Cancer in Japan). It was neither the case with gastric carcinoma without infiltration of the serosa nor for involvement of lymph node group 1.

Also, elsewhere results gathered from IORT supported Abe's assumption of improvement of survival rate for patients with advanced gastric cancer (stage III) [86]. However, Kraemling et al. as well as Sindelar et al. found no advantage concerning survival for a group of patients that underwent additional IORT [87]. Results from more comprehensive, prospective, randomized multicenter studies that could provide concrete prognostic criteria are so far not available.

Risks and Secondary Effects of IORT

As Abe observed already in 1974, the pancreas is the critical organ because of its closeness to the radiation field. Exposition to radiation is very difficult to avoid and manifests itself eventually in elevated liver and pancreas levels that are mostly reversible. In singular cases IORT is accompanied by pancreatitis [88]. These can be kept in calculable limits, so that the "Radiation Therapy Oncology Group" (RTOG) as well as NCI concluded that IORT poses no additional risk factor for the development of postoperative complications [89].

Free Circulating Tumor Cells

High rates of intraperitoneal recurrences limit despite radical tumor resection with correspondent extended lymph node dissection plus resection of infiltrated adjacent organs surgical success in treating gastric carcinoma. This prompts the idea of the existence of hematogene micro-metastases already at the time of surgery. Since elimination of these micro-metastases is the target of numerous adjuvant therapy concepts, early identification of micro-metastases appears to make sense. So far this has not been possible by using conventional diagnostics.

Novel methods, as e.g., immune-cytological verification procedure, provide in individual studies considerable success in verifying micrometastatic cells [90]. Implementation of monoclonal antibodies that are directed against epithelial antigens permit identification of individual epithelial tumor cells in the medulla, respectively, abdominal cavity [91].

Juhl and collaborators found in 52 % of patients' examined antibody-positive cells; at a rate of 43 %, a considerably more frequent involvement of the abdominal cavity with tumor cells in comparison with the medulla was registered. Bone metastases in cases of gastric-, colon- and pancreas carcinoma, as described already by Doerr et al. in 1973, are known to be quite rare [90]. The medulla was included in some investigations because it can be regarded as filter system of the blood stream—if tumor cells can be identified there. This serves as an indicator of hematogene dissemination of the primary tumor [92].

Earlier prevailing belief that hematogene dissemination occurs at an advanced stage of tumor only is contrasted by results of more recent studies [90]. Juhl and collaborators were able to identify disseminated tumor cells in stages IA and IB in 33 % of patients. This confirmed Nakajima's observation, dating back to the 1970s, of early micro-metastasis of gastric tumors [93]. According to his study, stage I tumor cells in the peritoneal cavity were detected with conventional methods in 3 % of patients.

Prognostic Significance of Free Circulating Tumor Cells

Inevitably, there is this question about the prognostic significance of free circulating tumor cells. Several studies correlated the immune-cytological results with tumor stages, respectively, the serosa

invasion of the tumor, and survival time to clarify the issue [94].

Juhl et al. managed to describe that verification of circulating tumor cells depended on the tumor stage. Accordingly, tumor cells in the abdominal cavity were more frequently detected in advanced than in early stages.

Concerning dependence of peritoneal dissemination on serosa invasion of the tumor, Boku and collaborators confirmed results achieved by Koga with the help of conventional methods of cytology back in the early 1980s [95]. With the S0-group, peritoneal tumor dissemination was 0 %; with the S1-group dissemination was 3.3 %; with the S2-group 15.7 %; with the S3-group 34.8 %. The difference between the results from the S3-group and the results from the other groups was statistically significant. Classification of serosa invasion was based on the following definition: S0 = no serosa invasion, S1 = suspicion of serosa invasion, S2 = definite serosa invasion, and S3 = infiltration of adjacent structures.

Schlimok and collaborators provided evidence of obviously higher incidence of tumor cells in the medulla in patients with loco-regionary lymph node involvement (38.9 %) than in patients without lymph node involvement (21.6 %). Besides, following the Laurén classification, they found more cumulative occurrence of tumor cells in the medulla of the diffuse type (44.0 %) than in the medulla of the intestinal type (29.8 %) [91]. Looking at R0-resected patients, Juhl et al. detected in 48 % of the cases an immune-cytological proof of disseminated tumor cells in the medulla (22 %), respectively, in the abdominal cavity (40 %). Jauch et al. detected in 55 out of 109 curatively operated patients (51 %) tumor cells in the medulla [96].

With the introduction of innovative surgery methods towards the end of the previous century, as, e.g., the laparoscopic/minimal invasive abdomen surgery on the one hand [97], and the endoscopic mucosal resection (EMR) in early cancer on the other, surgeons and gastroenterologists hoped to make a further contribution to the treatment of gastric cancer [98]. The advantage to be gained by minimal invasive surgery techniques should decrease stress for the immune system so that subsequently both immune-suppressive therapies as well as immune stimulating therapies can be implemented to greater effectiveness in the treatment of gastric cancer. While EMR is restricted to a tumor infiltration stage T1, SM1, size < 3 cm, laparoscopic surgery has no real limitations in terms of operable tumor stage.

Here and now, in the second decade of the twenty-first century, despite progress made, Billroth's summarizing words of August 1890 at the international congress in Berlin still ring true:

> I have no doubt that in case of continued diligent study an earlier detailed diagnosis will be possible, and that by perfecting methods and techniques we shall be able to reduce the effects of gastric cancer to a significant extent [99].

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Epidemiology of Gastric Cancer

2

Massimo Rugge, Matteo Fassan and David Y. Graham

Introduction

Despite its declining incidence, gastric cancer is globally, still, the third most common cause of cancer-related mortality [1–3]. It has been estimated that a million new gastric cancer cases were registered in 2008 [4]. Two in three of these cancers occurred in Eastern Asia, Eastern Europe, and South America, with a case fatality ratio of 78 %, as opposed to the 65 % of the industrialized world [5]. At diagnosis, virtually one in two gastric cancer patients present with advanced disease, with a 5-year survival rate lower than 30 % [6, 7].

Gastric cancers include a heterogeneous group of malignant epithelial lesions with a variety of predisposing conditions and etiological factors [8]. More than 95 % of the gastric cancers are adenocarcinomas, which are divided histologically into intestinal and diffuse histotypes. Squamous, adenosquamous, undifferentiated, and medullary carcinomas are less prevalent histotypes. Intestinal-type gastric cancer is by far the most common variant of gastric cancer (accounting for 50–70 % of the cases), and its geographical distribution overlaps that of the causative factor *Helicobacter pylori* (*H. pylori*) infection [9].

Historical Notes

In the fourth century BC, Hippocrates applied the term "cancer" ("Karkinos") to a gastric disease apparently consistent with the modern day description of a stomach malignancy [10]. In the first half of the nineteenth century, Cruveilhier and Rokitansky provided the first anatomical description of a gastric malignancy and described the connection between gastric ulcer and gastric cancer. In 1879, von den Velden reported the biological link between achlorhydria and gastric tumors [11–13]. As reported by Howard K Gray, the *Catalogue of the Library of the Surgeon General's Office of the United States* of 1892 listed 955 titles of papers dealing with cancer of the stomach. In the 20 years that followed, the number of scientific publications on gastric cancer rose to more than 1700. The extraordinary incidence of gastric cancer at that time prompted a great deal of research on gastritis, gastric acid secretion, and methods—other than autopsy—for diagnosing gastric cancer.

In the early twentieth century, Faber changed the course of histopathology with his early postmortem intragastric formalin administration, which "cleansed" microscopic observations of

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autolytic artifacts, providing histology-based evidence that "cancer in the stomach in most cases develops on the basis of a chronic gastritis" [14].

In the mid-twentieth century, Comfort assembled the available information, and thus linked gastric mucosa atrophy with hypoacidity, identifying chronic atrophic gastritis as the "cancerization field" in which most gastric cancers appeared [15].

With the advent of fiberoptic gastrointestinal endoscopy and *in vivo* histology, the knowledge of both the tumor and its anteceding lesions expanded further. Many epidemiological studies explored the relationship between gastritis and gastric cancer, generating the germinal information that was later pooled by Correa in his hypothesis of a "multi-step/multi-factorial oncogenic cascade" [16].

In 1983, Warren and Marshall reported that *H. pylori* infection caused chronic gastritis, and gastric cancer was recognized as an "infectious, epidemic disease" [17, 18]. This "infectious trait" may explain most of the epidemiological characteristics of gastric cancer, as well as providing the clinicobiological rationale for any attempt at primary and secondary gastric cancer prevention [19].

Gastric Cancer Histology and Its Epidemiological Implications

Gastric cancers are histologically heterogeneous, and their classification is generally based on the most prevalent histological phenotype (tubules, papillae, mucous lakes, solid nests/islands, undifferentiated epithelia). Several histological classifications have been suggested mainly for prognostic purposes. The most frequently applied internationally is the one proposed by Laurén in 1965 [20], which distinguished between two main gastric cancer histotypes—intestinal and diffuse (Fig. 2.1) (a mixed histotype is also considered). The intestinal histotype is by far the most common histology worldwide, and much more prevalent among "sporadic cancers." Its main etiological agent is *H. pylori*, and cancer morphogenesis is part of a multistep progression initiated by a longstanding inflammation, followed by mucosal atrophy with gastric gland intestinalization. Then, intestinalized glands may further progress to intraepithelial neoplasia (arising from intestinalized epithelia), and ultimately to intramucosal and advanced invasive adenocarcinoma. In the USA, a recent survey covering the years 1973–2000, demonstrated that the decline in gastric cancer applies specifically to the intestinal histotype, whereas cases of the diffuse vari-

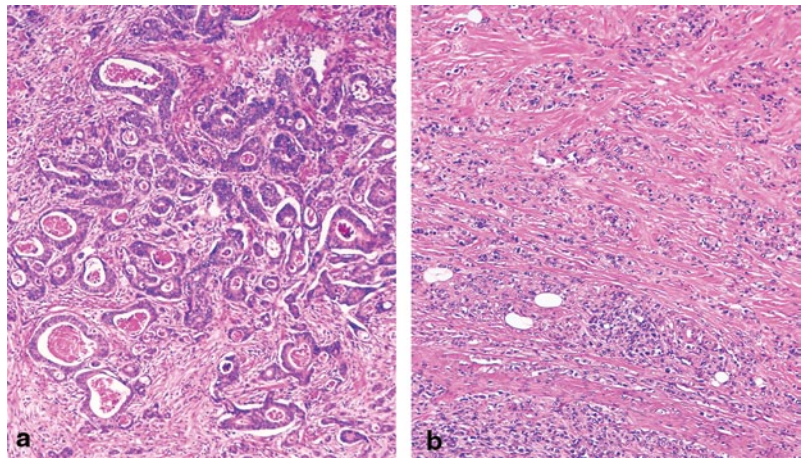

Fig. 2.1 Gastric cancer (GC) histotypes according to Laurèn classification. **a**. Intestinal-type GC: glandular cancer structures of different size infiltrating the gastric wall (H&E, original magnification 40×). **b** Diffuse-type GC: noncohesive cancer cells infiltrating the gastric wall, without forming glandular structures (H&E, original magnification 20×)

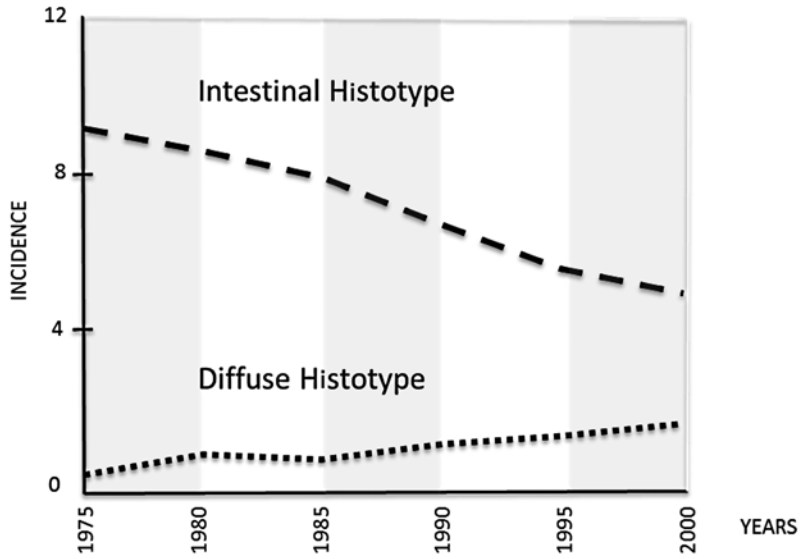

Fig. 2.2 In the USA, the incidence of the GC intestinal histotype progressively decreased between 1975 and 2000; during the same time interval, an increasing incidence of diffuse histotype was noted. (From Arch Pathol Lab Med. 2004; 128: 765–70; modified)

ant have gradually risen since 1973 (Fig. 2.2). On average, while the figures for the intestinal type have dropped by 2.4 % a year; for the diffuse variant, they have risen by 3.6 % a year [21].

Other widely used classifications include that of the World Health Organization (WHO) [9] and the one proposed by the Japanese Gastric Cancer Association [22].

Etiology

Gastric cancer is a multifactorial disease. It can be syndromic/hereditary, associated with specific mutational profiles [23–26]. Most frequently, however, gastric cancers are sporadic and stem from a progressive accumulation of genotypic and phenotypic changes triggered by longstanding gastritis, primarily due to *H. pylori* infection [27–29].

In 1994, the International Agency for Research on Cancer (IARC) recognized *H. pylori* infection as a type I carcinogen [30]. It has been estimated that *H. pylori* infection is responsible for more than 75 % of distal (antral) gastric cancers and associated with both types, intestinal and diffuse; its association with proximal (cardia-based) carcinomas is more dubious [31].

H. pylori is a Gram-negative spiral bacterium with a variety of mechanisms that enable it to colonize the gastric mucosa and evade or modify the host's immune response [32]. The infection is usually acquired in childhood and typically persists for decades unless it is treated and the bacterium is eradicated. The exact mechanisms behind the bacterium's transmission are still unknown, but it is believed to be transmitted person to person.

Multiple mechanisms have been described for the carcinogenesis associated with *H. pylori*, including inflammation, direct interactions with organisms that cause genetic instability in the host, and *H. pylori*-associated epigenetic alterations [33]. *H. pylori* differ in terms of their virulence. The most important factors influencing *H. pylori* virulence include a vacuolating toxin, VacA, *H. pylori* neutrophil-activating protein (NapA), and proteins encoded by the cag pathogenicity island [34].

H. pylori is believed to have a necessary, but not sufficient causative role in gastric cancer. For instance, the lifetime risk of gastriccancer in the

Japanese has been estimated at 11%, whereas gastric cancer is rare among South Africans or Southern Indians, despite a very high prevalence of *H. pylori* infection [35]. As discussed below, *H. pylori*-associated gastric cancer is closely associated with atrophic gastritis, which is associated in turn with environmental factors, and especially diet and gastric cancer incidence changes rapidly with migration or diet.

Epstein-Barr virus (EBV) is another infectious agent involved in gastric cancer, and several Asian, European, and American studies have consistently associated EBV infection with 5–16% of gastric cancers [36, 37]. Male patients were twice as likely to have EBV-positive tumors as female patients, and tumors arising in the proximal stomach were more than twice as likely to be EBV-positive as tumors in the antrum. No difference in the prevalence of EBV has been demonstrated between the intestinal and diffuse histological types, but a strong association (>90%) has been established between EBV infection and the uncommon lymphoepithelioma-like gastric cancer. The role of EBV in gastric carcinogenesis is, however, yet to be clarified.

Noninfectious Environmental Factors and Lifestyle Variables

Among the dietary factors, high salt intake has historically been associated with a higher risk of gastric cancer, mainly in association with *H. pylori* infection [8]. Many case-control studies consistently demonstrated a positive association between salted fish/meat, salted vegetables, and gastric cancer, and this association was recently confirmed in a systematic review of the available epidemiological data [38, 39].

A diet rich in meat has also been suggested as a risk factor in Europe. A large-scale European study found a significant correlation between meat consumption and distal gastric cancer, and this association was stronger in subjects infected with *H. pylori* [40].

Tobacco smoking is a risk factor for the onset of gastritis, ulcers, and both proximal and distal gastric cancers. It has been claimed that tobacco has an etiological role in up to 18% of gastric cancer cases, and there is evidence to support the interaction between tobacco smoking and *H. pylori* infection [41]. In European males and females, both, the intensity and the duration of smoking habits have been associated with the risk of gastric cancer, and proximal cancer in particular (HR=4.10) [41].

The available information on the etiological role of alcohol consumption is contradictory. A strong association was demonstrated by a Russian case-control study identifying a three-fold higher risk of cardia cancer among male heavy drinkers (OR 3.4; CI 1.2–10.2) [42]. On the other hand, a recent meta-analysis of 44 case control and 15 cohort studies (covering 34,500 cases of gastric cancer) showed that a light/moderate alcohol consumption coincided with an insignificant increase in this risk [43]. A low total body iron, in terms of serum ferritin levels, has also been associated with gastric cancer, but this is probably a spurious link since *H. pylori* is associated with iron deficiency (the virus would delete iron) [44].

Fruit and vegetables have consistently been attributed a protective role. In a prospective study on 70,000 subjects (139 with gastric cancer), a daily intake of 2–5 servings of fruit/vegetables resulted in a hazard ratio of 0.56 (95% CI: 0.34–0.93) when compared with less than one serving a day [45].

The protective effect of vitamin C is more controversial, some studies attributing vitamin supplementation of a protective role that is denied by others [46–48].

Host Factors

The risk of gastric cancer has been associated with numerous genetic polymorphisms, mainly involving inflammation-related genes (e.g., IL1B, IL1RN, IL10, and TNF) [8]. Both, interleukin (IL)-1β and tumor necrosis factor (TNF)-α, are powerful proinflammatory cytokines that also suppress gastric acid production. IL-10 is an anti-inflammatory cytokine that counteracts the effects of proinflammatory cytokines, and vari-

ants of IL10 have been identified that influence its production. Generally speaking, more virulent *H. pylori* strains and gene polymorphisms associated with an enhanced inflammatory reaction carry a greater risk.

The risk of developing gastric cancer is 2–10 times higher in subjects with a family history of gastric cancer [40]. Most familial cases are considered sporadic, however, and seem to be influenced by shared environmental factors, such as *H. pylori* infection, diet, and socioeconomic status. Gastric cancer can nonetheless develop as part of a familial cancer syndrome, such as hereditary diffuse gastric cancer syndrome, Lynch syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome, and Li-Fraumeni syndrome [49].

Hereditary, diffuse-type gastric cancer is a rare, autosomal dominant disorder responsible for 1–3 % of familial cases. This syndromic cancer is caused by various mutations of the gene encoding E-cadherin (*CDH1*), a cell adhesion protein essentialto maintaining the epithelial tissue architecture [50]. These mutations result in a 70–80 % lifetime risk of the onset of gastric cancer; hence, preventive gastrectomy has been suggested. Other conditions that raise the risk of gastric cancer are pernicious anemia, Menetrier's disease, and gastric stumps after gastric surgery.

Epidemiology

The global distribution of gastric cancer differs markedly from that of most other adult tumors. Like the majority of "environmental" cancers, the risk of gastric adenocarcinoma is very low in young age and gradually increases with age, reaching a plateau between 55 and 80 years (depending on the variable interaction of different risk factors) [9]. In general, gastric cancer rates are twice as high in men as in women.

The highest incidence rates in males are found in Eastern Asia (Korea, Mongolia, Japan, and China, with rates between 40 and 60 per 100,000 population), Eastern Europe (around 35 per 100,000), and some Latin American countries, especially Central America and the Andean Region, with rates between 20 and 30 per 100,000 population [8, 51]. Some of the lowest incidence rates are found in African countries (0.6–3/100,000) and more recently in North America (5–6/100,000) [8].

It is noteworthy that there are significant differences in the gastric cancer risk for different ethnic groups within the same geographical area [8, 51]. In the USA for example, Hispanics, African-Americans, and Native Indians are more affected than Caucasians [8]. These variations cannot be considered simply as ethnicity-related, however, due to the overlapping disparities in the socioeconomic status, which is also inversely related to both *H. pylori* prevalence andgastric cancer risk. Several studies conducted in different regions have consistently demonstrated that a low socioeconomic status is per se an adverse variable that raises the risk of (gastric) malignancy [52, 53].

The relevant impact of the "environmental etiological component" is further demonstrated by the lower gastric cancer risk described in the offspring of populations that migrate from high- to low-incidence continents (e.g., from Asia to North America) [54, 55].

In the past 50 years, the incidence rates of stomach cancer have been declining steadily in many parts of the world [27]. This is believed to be partly due to factors associated with the use of refrigerated foods, the availability of fresh fruits and vegetables, and a decrease in the use of salt (at the table and for food preservation). Other likely associated factors include a decrease in the prevalence of *H. pylori* infection in many countries and the decline in smoking in some industrialized countries [4].

Changing Trends in Incidence by Site

Albeit with some notable exceptions, the incidence of gastric cancer has fallen steadily all over the industrialized world [56]. Looking closer at these epidemiological trends, however, and distinguishing gastric malignancies by their topography, it has been consistently observed that gastric cancers have been "climbing" from the distal to the proximal stomach (Fig. 2.3) [57].

This phenomenon was initially attributed to an inconsistent recording of tumor topography, but it has been confirmed in many countries, and available data from the Surveillance, Epidemiology, and End Results (SEER) cancer registry program in the USA show an approximate 2.5-fold increase in the incidence of adenocarcinoma at the gastroesophageal junction from 1973 to 1992, with rates stabilizing in the past two decades. Similar proportional trends have been seen among subgroups stratified by race and gender, with significantly higher rates in white males [58–60].

Another phenomenon recently identified in the USA is an increase in the rate of distal gastric cancers in Caucasian adults of both sexes between 25 and 39 years old [8]. This rising trend has continued over the last three decades and its causes are still unknown [56]. In our experience (DYG), these patients are typically young recent immigrants from high incidence areas of Central and South America.

The Genetic Landscape of Gastric Cancer

The molecular profile of gastric cancer is heterogeneous, partly due to different classification systems being used, and also because most analyses have considered a very limited number of cases [50, 61]. As a result, despite the huge amount of data collected, no reliable, novel molecular markers have been introduced for use in secondary prevention strategies to date [50, 62, 63]. Efforts in this direction have gained strength, however, from the recent promising arrival on the scene of innovative technologies (next-generation sequencing [NGS], high-throughput microarray know-how) and the unexpected discovery of new classes of biomarkers (microRNA [miRNA], and long noncoding RNAs) [64, 65].

Whole genome sequencing studies have recently revealed new molecules and mechanisms involved in gastric cancers [23–25]. In particular, *RHOA* mutations have been identified as one of

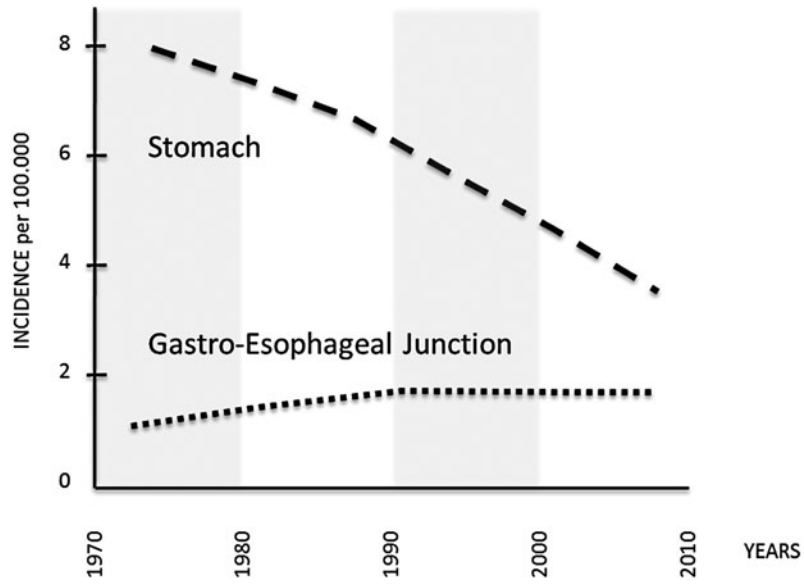

Fig. 2.3 Incidence of adenocarcinoma of the noncardia stomach, and gastroesophageal junction in the USA, 1973–2008 (per 100,000, adjusted for age, race, and sex to the 2000 US standard population, with Lowess smoothing; Data from the National Cancer Institute's SEER Program). (From Semin Radiat Oncol. 2013;23:3–9; modified)

the most important drivers of diffuse-type, but not intestinal-type tumors [24, 25]. Data on 295 primary gastric cancers involved in The Cancer Genome Atlas (TCGA) project point to a new four-tiered molecular classification of gastric cancers: (i) gastric cancers positive for Epstein-Barr virus, which display recurrent *PIK3CA* mutations, extreme DNA hypermethylation, and amplification of *JAK2, PD-L1* and *PD-L2*; (ii) microsatellite unstable gastric cancers, which show elevated mutation rates; (iii) genomically stable gastric cancers, which are enriched for the diffuse histological variant and mutations of *RHOA* or fusions involving RHO-family GTPase-activating proteins; and (iv) gastric cancers with chromosomal instability, which show marked aneuploidy and focal amplification of receptor tyrosine kinases [23].

Whole exome sequencing studies have further dissected gastric intestinal-type carcinogenesis [66, 67]. The genes found frequently mutated included *TP53, PIK3CA, FAT4*, and *ARID1A* [66, 67]. The latter two have been identified as novel gastric cancer markers. *FAT4* is a member of the cadherin gene family, which is mutated in 5% and deleted in 4% of gastric cancers [67]. The protein encoded by *ARID1A* is an accessory subunit of the SWI-SNF chromatin remodeling complex involved in processes of DNA repair, differentiation and development, as well as in the homeostasis of cell proliferation [68]. Mutations in chromatin remodeling genes, such as *ARID1A, MLL3*, and *MLL*, have been found in 47% of gastric cancers [7].

Alterations of the *TP53* gene are associated throughout the spectrum of histological lesions involved in gastric oncogenesis. Loss of heterozygosity at the *TP53* locus has been demonstrated in 14% of a series of gastric IM and in 22% of dysplastic lesions [69]. In a recent series of 15 matched high-grade IEN and early gastric cancers, NGS analysis of hotspot regions in 50 cancer-associated genes disclosed a molecular similarity between the two lesions, and further supported a relevant role for *TP53* in progression to the invasive phenotype [65].

Epigenetic mechanisms have been found to have a central role in both the earliest changes (i.e., atrophic gastritis and intestinal metaplasia) and the advanced stages of cancer [70, 71]. Studies on *H. pylori* and Epstein-Barr virus infection have shown that the carcinogenic effect of both these pathogens is reinforced by inducing methylation changes in the gastric mucosa [72–74]. The methylation status in the tumor tissue resembles the patterns found in serum samples, so methylation status has the potential to become a noninvasive oncological marker exploitable in the early diagnosis of gastric cancer, and a novel target for cancer prevention [75].

As in other human cancers, aberrant miRNA expression is a hallmark of gastric cancer [64]. Ueda et al. recently performed the largest study to date on gastric cancers [76]. Using a sizable number of gastric cancer tissues paired with non-tumor samples, the authors identified 22 up- and 13 down-regulated miRNAs. Using the pattern of the 19 most significantly dysregulated miRNAs, it was also possible to discriminate gastric cancers according to their histological type. In particular, cluster analyses showed that miR-105, miR-100, miR-125b, miR-199b, miR-99a, miR-143, miR-145, and miR-133a were upregulated in diffuse-type gastric cancer, while miR-373-3p, miR-498, miR-202-3, and miR-494 were upregulated in intestinal-type lesions. Of note, miRNAs can be used as noninvasive biomarkers of gastric cancer [77], being readily and reproducibly detectable in various body specimens including blood, gastric fluids, feces, saliva, and others.

Gastric Cancer Secondary Prevention

Non-self-limiting chronic inflammation, mainly due to *H. pylori* infection [13, 19, 78], triggers both genotypic and phenotypic changes in the gastric mucosa. This process leads to an absolute loss of resident glands and/or to the native glands being replaced by inappropriate (metaplastic) glandular units (i.e., atrophic gastritis). The metaplastic variant of atrophy includes two main phenotypes: pseudo-pyloric metaplasia and intestinal metaplasia (IM). The atrophic transformation of the gastric mucosa provides the cancerization field in which (intestinal type) gastric cancer usually develops [27, 28, 78].

Metaplastic/atrophic glands are biologically "unstable" and prone to further dedifferentiation. This situation results in "neo-epithelia" harboring most of the biological traits of neoplastic cells. These (already) neoplastic epithelia lack the capacity for invasion, however, remaining topographically confined within the basal membrane of the glandular structure (i.e., intraglandular neoplasia (IGN); synonyms: intraepithelial neoplasia (IEN), noninvasive neoplasia (NiN); and formerly called dysplasia) [79]. Further progression of the molecular derangements, coupled with a proliferative advantage, loss of cell-to-cell adhesion, and the development of a capacity for invasion ultimately result in (early) invasive adenocarcinoma [50].

This natural history provides the rationale behind multidisciplinary strategies for cancer primary and secondary prevention [8, 28]. Several operative inconsistencies significantly influence efforts to anticipate gastric cancer detection, however, including: (i) the reliability of clinical/serological data used to assess gastric precancerous conditions; (ii) the endoscopic assessment of preneoplastic lesions; (iii) the biopsy sampling protocols applied; (iv) discrepancies in the histological classifications; and (v) interobserver variability in histology reporting.

In *H. pylori*-associated gastritis, atrophic changes are seen earlier in the angular (transitional) mucosa, involving the distal stomach only later on (i.e., antrally restricted atrophic gastritis), and finally spreading towards the (cranial) oxyntic mucosa (a condition sometimes called multifocal atrophic gastritis (MAG), or atrophic pan-gastritis) [80]. It takes years to progress from nonatrophic inflammatory disease to its atrophic counterpart, consistently with the rising prevalence of atrophic gastritis with age. The distal-to-cranial spreading of atrophic changes can also be confidently considered an indication of a stepwise progression of the atrophic disease. Consistently with this hypothesis on the disease's natural history, Japanese researchers identify oxyntic atrophy as the most advanced stage of *H. pylori*-associated gastritis.

Several studies have consistently associated the severity/topography of gastric atrophy with the risk of gastric cancer [8, 27, 28, 78, 81]. Built on the seminal experience of the Sydney System, Histological Division [82, 83], the histological phenotyping of gastritis implies a topography-based assessment of the inflammatory/atrophic changes involved. As a consequence, biopsy specimens should be obtained from each of the two mucosal compartments (e.g., three biopsy samples from the antrum—including the *incisura angularis*—and two from the gastric body) [19].

The "descriptive" philosophy behind the Sydney System has recently been replaced by a new approach to gastritis histology reporting [19]. The aim of the new diagnostic format (gastritis staging) is to enable a more definitive and clinically more readily perceptible stratification of the gastritis-associated risk of gastric cancer. The new staging format has yet to be included in the guidelines addressing the Management of Gastric Precancerous Conditions/Lesions (MAPS). These guidelines recognize the prognostic reliability of the staging approach, but base their operativerecommendations on the topographical "spread" of atrophy/metaplasia alone, without considering the (more significant) prognostic message in gastritis staging [62].

Two related staging systems have been proposed and are in current clinical use: the OLGA and the OLGIM [84–86]. Both, OLGA and OLGIM, distinguish between four stages of gastritis (stages 0 to IV), associated with a progressively increasing risk of gastric cancer. The first staging system was presented in 2005 by an international group of pathologists and gastroenterologists (OLGA is an acronym for "Operative Link on Gastritis Assessment") [86]. According to the OLGA approach, the stage of gastritis stems from the combination of the atrophy scores for the distal stomach with those assessed in the biopsy samples obtained from the proximal gastric mucosa [84]. This stage indicates the individual's likelihood of developing a malignant neoplasia, and the vast majority of cases of cancer are expected to develop in patients in stages III and IV [87]. The stage of the organic lesions interestingly correlates with "functional" parameters of the gastric mucosa, and in particular with serum pepsinogens [88]. This correlation between "or-

ganic" and "functional" gastric disease may be of paramount importance when serologically selecting atrophic patients in whom endoscopy/biopsy procedures can be used as part of any gastric cancer secondary prevention effort.

A simplified staging system (OLGIM) focuses on the score/topography of intestinal metaplasia within the antral and corpus mucosa [85]. Which of the two staging approaches is more efficient in clinical practice, is still a debated issue; but both are consistent with the clinical priority of stratifying gastritis patients by their cancer risk [85, 89, 90]. Both systems identify stage III/IV patients as carrying a higher cancer risk, and consistently only associate the specific recommendation for endoscopy/biopsy surveillance with this (restricted) population. The prognostic value of gastritis staging, already recognized by the Maastricht IV Consensus Conference [91], has been recently confirmed by the "Kyoto GlobalConsensus Meeting on *H. pylori* gastritis" (Kyoto 2014).

Conclusions

Despite its declining incidence, gastric cancer is still a major healthcare issue, associated with high mortality rates; hence, the need for more reliable strategies for both primary and secondary cancer prevention.

Based on the natural history of cancer, primary gastric cancer prevention relies mostly on the eradication of *H. pylori*, the main oncogenic agent. Secondary prevention strategies demand a more extensive implementation of serological tests, which have proved reliable in identifying patient populations eligible for second-level diagnostic procedures (and endoscopy, in particular).

For the time being, the contribution of non-invasive molecular biology tests is minimal, but the clinical reliability of several molecular markers, including miRNA signatures, and the clinical applicability of NGS studies are currently under investigation.

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Molecular Mechanisms in Gastric Carcinogenesis

3

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Introduction

Gastric cancer remains an uncommon neoplasm in the Western countries. However, globally, it remains the second leading cause of cancer-related death in both men and women and is ranked the fourth most common malignancy worldwide. Accordingly, the burden of mortality is significant and is expected to encompass approximately 750,000 individuals globally [1, 2]. In keeping with this statistic, global current 5-year survival rates are only 20–30 % [1, 3, 4].

Current curative intent treatment strategies in the management of resectable gastric cancer include loco-regional control through surgical resection and the limitation of systemic recurrence via cytotoxic 5-FU-based chemotherapeutic regimens [4]. Unfortunately, the management of non-resectable disease remains largely palliative, but frequently includes both medical and surgical approaches [3]. Despite advances in both of these modalities, the survival rate for patients with gastric cancer has only moderately improved over the past several decades and appears to have reached a plateau [5–7]. While the factors underlying this observation remain incompletely understood, a disconnect in the conceptualization of Gastric cancer (GC) at the clinical and basic scientific levels have begun to emerge [8]. The development of gastric cancer is a multifactorial process arising through the complex interplay of environmental and genetic factors over a patient's lifetime [1, 9, 10]. The net result is the aberrant expression of oncogenic and tumor suppressor genes leading to unregulated cell growth and the ability for dissemination ultimately leading to clinically apparent metastases [11, 12]. At the clinical level, however, gastric cancers are currently classified with respect to their anatomic location [antrum, body, cardia] and their histology [intestinal and diffuse] [8]. This nomenclature fails to take into account the potential for molecular aberrations at the cellular level that can have profound implications with regard to the patient's outcome. Furthermore, current evidence demonstrates that the genetic and epigenetic changes underlying the emergence, development, and behavior of GC are far more heterogeneous than contemporary clinical classification systems indicate [13–16]. A detailed understanding of the molecular biology behind the neoplastic phenotype is therefore essential to the development of more effective therapies. Current evidence from genomic analysis of GC samples and paired normal tissue reveals a vast and heterogeneous array of abnormalities in a number of fundamental cellular pathways [16, 17]. Furthermore, observed genetic alterations are

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not limited to the coding regions of genes, as diverse epigenetic alterations have been described in the context of GC [14, 15, 18]. Accordingly, the aim of the present review is to highlight some of the basic molecular mechanisms identified to date that drive this devastating neoplastic process.

Genetic Alterations in Gastric Cancer

Whole genome sequencing has permitted the identification of a vast number of genetic alterations in the gastric neoplastic tissue [16, 19–21]. Because, current clinical classification and prognostication in GC relies on histologic characterization to a large extent, a number of genetic studies have described the observed molecular alterations along these lines. While the sheer number of genes identified is vast, their elucidation has permitted significant headway with respect to the targeted therapies to be made [22, 23]. In addition, patterns in gene expression profiles have begun to emerge, offering the potential to classify GC tumor types along molecular, as opposed to histopathologic lines [13, 17]. The potential for more personalized, potentially effective therapies is inherent to such classification [11].

Specific Genomic Aberrations in Gastric Cancer

The study by Wang et al. represents perhaps the largest and most complete study to date, outlining the genetic changes associated with a number of GC types in a cohort of 100 patients and controls [16]. Genomic analysis revealed the presence of a number of mutations in genes thought to underlie the malignant phenotype; so called driver mutations. Driver mutations are postulated to impart a survival advantage to a particular clone, leading to its expansion and development [16]. Accordingly, their role is worth highlighting. Such mutations were found within both previously described and novel groups of genes. Among previously described genes, the authors demonstrate a high frequency of mutation within TP53, CTNNB1, ARID1A, and CDH1. In addition, the authors demonstrated a high frequency of mutation in less well-described genes including MUC6 RNF43, CTNNA2, GLI3, TGF-β family proteins, such as TGF-β, ELF3 and SMAD4, and RHOA.

Each of these proteins plays an important role in tumor development and progression (described below). In addition, the identification of these gene products as drivers of gastric carcinogenesis implicates several important signal transduction pathways, demonstrating considerable overlap with respect to their individual genetic members. These include the adherens, *Wnt*, and TGF-β pathways [16].

Specific Driver Mutations

Some of the driver mutations identified by Wang et al. involved proteins so ubiquitously involved in cellular function that their classification within a single pathway is difficult. These include TP53, MUC6, and ARID1A [16, 20, 21].

TP53 TP53 mutations have previously been identified as one of the most common genetic aberrations affecting patients with GC [21, 24, 25]. This critical tumor suppressor acts to induce cell cycle arrest, apoptosis, and senescence in response to a multitude of environmental stresses [24]. Alteration of TP53 function has been demonstrated at the genetic as well as epigenetic levels, with aberrant methylation of downstream genes in a large proportion of GC patients in addition to frequently observed mutations. For example, Zhang et al. demonstrated a frequency of mutation in TP53 in up to 73% of patients studied in their cohort [21]. Yoda et al. demonstrated TP53 inactivation in 35% of patients studied via point mutation. However, aberrant methylation of 24 downstream genes demonstrated the potential to negatively affect p53 signaling, which contributes to unregulated tumor proliferation, growth, and survival [25]. Taken together these results demonstrate that even in the absence of inactivating mutations, protein expression can be affected in multiple ways.

MUC6 High rates of MUC 6 inactivating genetic alterations are observed in both intestinal and diffuse/mixed type gastric tumors [16]. Secretion of MUC6 is thought to play a protective

role in the gastric mucosa with regards to environmental insults. Down regulation of MUC 6 is observed following infection with H. *pylori* during the development of IM and in GC [26]. In addition, MUC6 expression in GC correlates negatively with tumor size, depth of invasion, presence of LN metastases, and in the context of diffuse as opposed to intestinal tumor types [27]. These findings, in conjunction with the pattern of genetic alterations leading to its down regulation in GC, suggest that MUC 6 may act as a tumor suppressor. This function may be mediated by the presence of αGLC-NAC residues along with the MUC6 protein backbone [27, 28]. In keeping with this hypothesis, mice deficient for αGLC-NAC were found to demonstrate increased inflammatory infiltration of the gastric mucosa with macrophages, and neutrophils, with a concomitant increase in levels of inflammatory cytokines [28]. This process is postulated to facilitate tumor growth and development. Additional clinical evidence for this stems from the observation that a large proportion (~40%) of GC that do exhibit MUC6 expression demonstrate low levels of GLcNAC expression [27, 28].

ARID1A ARID1A encodes an ATP-dependent chromatin remodeling protein required for the transcription of a number of genes normally repressed by chromatin structure [16, 20, 21]. Functional analysis of ARID1A protein knockdown by Zang et al. demonstrated enhanced proliferation of GC cell lines, which was associated with a concomitant rise in cellular levels of E2F1 and CCNE1 (cyclin E1) mRNA [21]. These observations have suggested that ARID1A protein acts to regulate cell cycle progression [21]. In addition, it may function in conjunction with p53 in order to repress p21 and limit progress from G1 to S phase [21].

Pathways Frequently Harboring Driver Mutations

Adherens Pathway (CTNNA2 CTNNB CDH1 RHOA) Adherens junctions are dynamic structures located on the cell surface, which in part define a cells apical-basal axis [29]. In addition to the mediating interactions between adjacent cells, these structures act to transduce signals from the extracellular milieu to the nucleus leading to gene transcription [29]. Gastric cancer driver mutations identified within the genes of this pathway include CDH1, CTNNB1, CTNNA1, and RHOA [16].

CDH1 CDH1 encodes E-cadherin, whose dysfunction has been extensively demonstrated in GC [16, 25]. Hereditary forms of diffuse type GC have been demonstrated as a result of germ line mutations and disruption of normal E-cadherin function [30]. In fact, CDH1 germ line mutations are associated with an 80% lifetime risk for the development of GC, precipitating prophylactic gastrectomy in appropriately selected patients [30]. Under physiologic conditions, E-cadherin modulates cell-cell adhesion via homophillic interactions [29]. Reduced expression or function of E-cadherin is thought to facilitate detachment of cell-cell adhesion, which may underlie some of the early steps required for invasion and ultimately metastasis [29]. Accordingly, sporadic mutations have been demonstrated as a result of insertions, deletions, and frame shift mutations leading to truncated or otherwise non-functional E-cadherin protein [16, 21, 25, 29–31].

CTNNB1 CTNNB1 encodes β-catenin, which functions in the formation of adherens junctions by serving as a bridge between cadherin molecules, at their cytoplasmic tail, and the actin cytoskeleton [29]. This is achieved via its concomitant association with the intracellular portion of E-cadherin and α-catenin [29]. Following mechanical stimulation at the cell surface, β-catenin can become phosphorylated, disrupting its association with E-cadherin and leading to its nuclear localization where it functions as a transcription factor [29]. In the context of malignancy, genetic lesions in β-catenin can result in its aberrant nuclear localization leading to transcription of oncogenes such as MYC [32]. In addition, β-catenin mutations can result in impaired cellular aggregation through the abolition of E-cadherin function despite its normal structure [29, 31].

CTNNA2 Mutations of CTNNA2 were similarly observed to represent driver mutations in the human GC [16]. CTNNA2 encodes catenin-α2, which, as previously stated, plays an important role in the regulation of β-catenin signaling [29]. Mutations have been observed in a number of malignancies in addition to GC including laryngeal carcinoma, gliomas and urothelial cancers [33–36]. Inactivating mutations have been shown to increase the neoplastic cell migratory and invasive capabilities [34, 35]. These phenotypic observations are associated with enhanced nuclear translocation of β-catenin and consequent transcription [34]. These results suggest that CTNNA2 may act as a tumor suppressor by preventing β-catenin nuclear translocation resulting in the maintenance of cell-cell adherence and the inhibition of migratory and invasive behaviors.

RHOA In diffuse type gastric tumors, in particular, recurrent mutations are observed within RHOA [16]. Diffuse and mixed type tumors were found to harbor up to 13 different mutations in 14.3 and 7.8% of patients in a cohort of 167 GC patients respectively. Conversely, no patients with intestinal type mutations were found to harbor any RHOA mutations [16]. This gene encodes a 21 kDa Rho GTPase, which is localized within the cytoplasm. It exerts diverse functions, playing a role in actin organization, cell motility, cell polarity, transcriptional regulation, and cell cycle progression [37]. The mutations associated with diffuse type tumors suggested loss of function, with the result being impaired interaction of RhoA with its downstream effector proteins and consequent downstream signaling [16]. Diffuse type tumors bearing these mutations tended to demonstrate poor differentiation and were found to localize predominantly within the body and the antrum. The functional consequence of RhoA mutation was a resistance to anoikis, imparting transfected murine cells with the ability to grow as isolated islands within a Matrigel matrix [16]. This phenotypic feature is thought to be an important property of diffuse type tumors, contributing to their growth and progression [16].

***Wnt* Pathway—(CTNNB1, RNF43)** The *Wnt* signal transduction pathway is a highly conserved signaling cascade mediating fundamental cellular and biologic processes including growth, development, polarity, and organogenesis [38]. The *Wnt* signaling pathway appears to play an important role in the pathogenesis of GC as well [16, 25]. This is evidenced by the frequent observation of aberrant function in a number of the signaling proteins involved in this pathway. Key driver mutations identified affect CTNNB1 and RNF43 [16].

CTNNB1 As previously stated, CTNNB1 encodes β-catenin, which plays an important regulatory role in the transcription of *Wnt* pathway gene products; namely, LEF/TCF family transcription factors [29]. Such transcription is able to occur following the nuclear translocation of β-catenin in the nucleus [29]. Nuclear localization of this transcription factor is associated with the intestinal phenotype in patients with gastric adenocarcinoma and has been observed in a significant proportion (~30%) of GC patients overall [39, 40]. Nuclear localization is tightly controlled, such that under resting conditions, β-catenin remains sequestered within the cytoplasm within axin:APC agglomerates, termed the destruction complex [29]. This interaction facilitates its phosphorylation by GSK3, targeting β-catenin for ubiquitin-mediated degradation [12, 29]. Mutations disrupting the phosphorylation of β-catenin by GSK3, or leading to inappropriate *Wnt* signaling, either up or downstream of β-catenin, result in its inappropriate nuclear accumulation and/or transcription of *Wnt* pathway target genes [29, 39]. The consequences of inappropriate pathway activation in the context of malignancy include increased proliferation, invasion, and the epithelial to mesenchymal transition [41, 42].

RNF43 Pathway deregulation can occur at any step of the *Wnt* signal transduction cascade [41, 42]. Along these lines, a high frequency of mutation in the RNF43 gene has been observed, identifying it as another driver mutation in the GC [16]. This gene encodes an E3 ubiquitin ligase

that can function to target Frizzled receptors for proteolytic degradation [16, 43]. Accordingly, this protein is thought to function as a tumor suppressor [16]. Evidence for this stems from the observation that deletion of this protein in mice results in the rapid development of colorectal adenomas [43]. Conversely, induced expression of this protein in tumor cell lines results in degradation of *Wnt* receptors via ubiquitination associated with a concomitant decrease in β-catenin mediated signaling [16, 43].

TGF-β Pathway Multiple TGF-β family genes demonstrate mutations in primary human GC, implicating them as possible drivers in gastric carcinogenesis [16]. These include TGFBR2, SMAD4, and ELF 3 [16]. Aberrant TGF-β signaling has been demonstrated in a number of malignancies in addition to GC including colorectal, pancreatic, and hepatic tumors [44–46]. Decreased responsiveness to TGF-β in GC has been linked to the development of more aggressive tumor phenotypes and may promote metastasis via its role in immunosuppression, EMT, and enhanced angiogenesis [41, 47]. Multiple studies have demonstrated TGFBR2 inactivating mutations in GC [16, 48–51]. Similar observations have been made regarding SMAD 4 mutations, resulting in diminished signal transduction following TGF receptor-ligand interaction [16, 51, 52].

As with all of the signaling pathways discussed thus far, aberrant function can arise secondary to any number of abnormalities in any member of the transduction cascade in question. Along these lines, decreased TGFBR2 expression can occur following inactivating mutations to ELF3 [53]. This gene encodes a transcription factor that can induce TGFBR2 receptor expression [16, 53, 54]. To date, all mutations observed in ELF3 in the context of GC as described by Wang et al. result in inactivation [16].

Taken together, these results demonstrate the diversity of genetic alterations accumulating within seemingly homogenous tumor types. Furthermore, they highlight the diversity in the cellular consequences associated with the aberrant function of even a single protein. A detailed understanding of the molecular events that drive tumor progression is therefore imperative with respect to the development of effective treatment modalities. Furthermore, these findings potentially underscore the disappointing results associated with a "one size fits all" approach to chemotherapy traditionally employed in the treatment of gastric malignancies.

Somatic Copy Number Aberrations and Consequent Driver Alterations—Treatment Implications

Comparisons between normal and malignant gastric tissue revealed the presence of large numbers of chromosomal alterations leading to gains or losses in predominantly intestinal type tumors compared to diffuse/mixed and normal gastric tissue [16]. The consequence of such chromosomal alterations is the disruption of a number of genes including putative oncogenic drivers. Among them, Wang et al. identified proteins currently under investigation as targets for molecular based therapies in GC including MET and ERBB2 [16, 22]. While a full discussion of these proteins in the context of GC is beyond the scope of this chapter, their contribution to gastric carcinogenesis is worth highlighting.

MET

cMET is a receptor tyrosine kinase whose endogenous ligand is hepatocyte growth factor (HGF) [55]. This proto-oncogene is activated in a variety of human cancers, including approximately 10% of human gastric carcinomas [56, 57]. Activation has been observed to occur via overexpression of HGF, amplification of the c-MET receptor, up regulated transcription and translation of cMET and via acquisition of mutations leading to constitutive activation [55, 56, 58–60]. Paracrine signaling through c-MET has been shown to induce migration, invasion, and resistance to apoptosis both in vitro and in vivo[57]. Taken together, these observations highlight its potential as a therapeutic target.

Signaling via MET as a result of interaction with HGF results in signal transduction through

the activation of a number of downstream signaling cascades [56]. These include the RAS-REF-MEK-ERK and PI3-Akt pathways [56]. These signaling events have been shown to translate into a number of cellular processes including proliferation, inhibition of apoptosis and anoikis, and cellular spreading and migration. Together, these cellular events have been termed "invasive growth" and are postulated to be sufficient to promote tumor growth and progression as demonstrated in a number of experimental models [56].

The demonstration that MET activation appears to promote tumor progression in animal models does have support from human studies. Soman et al. determined the presence of the activating TPR MET mutation in 22 human samples [61]. These included both preneoplastic lesions such as intestinal metaplasia as well as overt carcinoma. Overall, the authors demonstrated positivity in 12/22 (54%) samples. In addition, the analysis of 4 cell lines in vitro derived from human gastric cancers similarly demonstrated positivity for this activating c-MET mutation. Despite the small number of patients assessed, the results of this study serve as a proof of concept in human disease for a possible role of aberrant cMET signaling in human gastric cancer [61].

Since the study by Soman et al., multiple reports of C-MET overexpression in human gastric cancers have been made. As previously stated, the mechanisms by which excessive c-MET signaling occur are multiple and in some cases likely interrelated. These include HGF overexpression, CMET gene amplification, MET chromosomal amplifications, germ line, and somatic met mutations and chromosomal translocations [57].

Activation of the c-MET receptor by its cognate ligand is associated with receptor dimerization and autophosphorylation [57]. This results in the recruitment of a number of adaptor proteins ultimately leading to activation of intracellular signaling cascades highlighted previously. One of the major phosphorylation sites associated with receptor activation is tyrosine 1235 (Y1235). Immunohistochemical analysis of receptor activation status is thus possible by detection of the c-MET receptor in this particular phosphorylation state (p-MET). Inoue et al. exploited this biologic feature in order to demonstrate receptor activation status within malignant as opposed to benign tissue in gastric cancer patients [62].

HGF overexpression can induce receptor activation in certain instances [55]. HGF is produced predominantly by stromal cells, and is therefore believed to exert many of its effects in a paracrine manner [55, 63]. Basic scientific evidence supports this hypothesis. For example, Chen et al. demonstrates that exogenous administration of HGF supports SC-M1 gastric cancer cell growth in vitro. In vivo, the authors demonstrate a similar effect with regard to SC-M1 tumor growth in a murine model of gastric carcinoma [63]. As in human disease, activation of the c-MET receptor by exposure to HGF is associated with phosphorylation at Y1235 [63]. These results further implicate HGF overexpression as a potential important contributor to tumor cell development.

Clinical observations have demonstrated elevated levels of HGF in patients with gastric cancer, both locally within tumor tissue and systemically via its quantification in serum [55]. For example, Wu et al. characterized the expression of HGF in tumor samples derived from 32 patients with gastric cancer. The authors demonstrated HGF positivity in 87.5% of patients, which correlated with clinical outcome. These patients demonstrated diminished survival associated with strong HGF positivity [RR 15.9 $p=0.01$]. Quantitative assessment of serum HGF in gastric cancer patients demonstrates elevated levels, which correlate with patient outcome [64]. A study by the same authors described serum HGF quantity in 80 patients with gastric carcinoma and 51 healthy subjects [64]. A significant increase in serum HGF quantity was observed in gastric cancer patients with a mean serum concentration of 0.30 ng/ml versus healthy controls (0.22 ng/ml, $p=0.005$). The authors also demonstrated that this increase was directly related to tumor stage leading them to hypothesize that HGF itself is involved in tumor progression [64].

In keeping with this hypothesis, Tanaka et al. highlighted the potential utility of serum HGF as a biomarker of metastasis in patients with early

stage gastric cancer [65]. The authors quantitatively assessed serum levels of HGF in 30 patients with early stage disease. Compared to healthy controls, patients with early stage gastric cancer demonstrate significantly higher levels of HGF (0.24 versus 0.174 ng/ml $p=0.0488$). Furthermore, patients with early stage disease and small tumors (<20 mm) who harbor clinically occult lymph node metastases demonstrate higher circulating levels of serum HGF compared to those that do not (0.442 versus 0.258 ng/ml $p=0.0326$) [65].

What remains unclear based on the results outlined thus far is whether HGF is directly responsible for tumor progression or if its increased production is a by-product of tumor progression itself. Early preclinical studies appear to support the former [58]. For example, the seminal article by Cao et al. demonstrated that neutralization of HGF prevents the growth of MET dependent cell lines both in vitro and in vivo [58]. Similarly, systemic administration of Rilotumumab, a humanized monoclonal HGF neutralizing antibody, inhibits progression of U-87 murine tumors [66].

Rilotumumab has demonstrated promise in a phase 2 clinical trial for the treatment of locally advanced and metastatic gastric cancer [67]. In the study by Iveson et al., 120 patients with locally advanced or metastatic gastric or esophagogastric cancers were randomized to receive Rilotumumab in conjunction with ECX or ECX+ placebo. In patients with cMET overexpressing tumors, HGF inhibition was associated with a significant improvement in overall survival and a trend towards improved progression free survival compared to standard treatment and placebo alone (median OS 11.1 versus 5.7 months, [HR 0.29 CI 0.11–0.76] and median PFS 6.9 versus 4.6 months [HR 0.53 CI 0.25–1.13] respectively) [67].

MET overexpression without mutation or amplification appears to be the most common mechanism underlying aberrant MET signaling in gastric cancer. Overall, MET overexpression has been documented in up to approximately 70% of gastric cancers. Drebber et al. following immunohistochemical analysis of gastric carcinoma samples from 114 patients demonstrated strong staining for c-MET in approximately 74% of samples [68]. Furthermore, c-MET expression significantly correlated with reduced survival in both univariate and multivariate analyses [68]. Janjigian et al. similarly demonstrated high rates of c-MET protein expression in gastric cancers (63%) despite relatively low rates of genetic amplification (6.6%) [69]. Nakajima et al. assessed c-MET overexpression and amplification in 128 gastric cancer specimens by employing immunohistochemistry and Southern blot analysis [70]. As in the study by Janjigian et al., a higher frequency of overexpression versus amplification was observed. C-MET protein overexpression was observed in 46.1% of patients with amplification identified in only 10% of patients [69]. Wu et al. analyzed 120 primary gastric cancer specimens and determined the presence of c-MET overexpression in approximately 66% of them. Of particular significance, the authors identified a high rate of p-MET positivity (59%) suggesting activation of MET tyrosine kinase activity [71]. In keeping with the results of previous studies, MET overexpression was found to represent an independent marker of poor prognosis [71].

Interestingly, considerable variation in the quantification of p-MET expression is been noted within gastric cancer patients from different populations [69, 71]. The study by Wu et al. comprised a predominantly Eastern population in whom MET phosphorylation was quite prominent [71]. Conversely, the study by Janjigian et al. determined p-MET prevalence at 0% in a Western population [69]. Taken together, this data suggests that MET overexpression in the absence of amplification is a common phenomenon in gastric cancer. Furthermore, this negatively impacts the patient's survival, thus supporting a role for MET-directed therapies in gastric cancer patients. Accordingly, a number of studies in gastric cancer patients are currently underway and summarized in (Table 3.1).

HER2

Human epidermal growth factor receptor 2 (HER2) is overexpressed in several types of human cancers, and has become a well-established player in the pathogenesis of up to 54%

Table 3.1 Overview of phase I, II, and III compounds, their targets, and preliminary findings. (Table adapted from Jorgensen et al. [104] with permission from Baishideng Publishing Group Inc.)

Clinical phase	Compound	Type of compound	Target	Study details +/- preliminary findings
I	MGAH22	mAb	HER2	Dose escalation study of MGAH22 in patients with refractory HER2-positive breast cancer and patients with other HER2-positive carcinomas [including gastric] for whom no standard therapy is available is currently recruiting patients [124]
I/II	HM781-36B [Poziotinib]	Small molecule, pan-HER TKI	HER1, HER2, and HER4	A Phase I-II Study of HM781-36B[Poziotinib]Combined with paclitaxel and trastuzumab in HER-2-positive advanced gastric cancer is currently in the recruitment phase
II	MM-111	Bi-specific Ab	HER2 and HER3	A randomized, open label, Phase 2 Study of MM-111 and paclitaxel with trastuzumab in patients with HER2-positive gastric cancer who have failed first line therapy is currently recruiting participants (estimated enrollment: 120) [125]
	ASLAN001	Small molecule, pan-HER TKI	HER1, HER2, and HER4	ASLAN Pharmaceuticals confirmed biological activity of ASLAN001 in patients with recurrent/metastatic HER-2-positive gastric cancer. Plans to begin a randomized phase 2b study are underway [126, 127]
	Dacomitinib	Irreversible pan-HER TKI	HER1 and HER2	7.4 % response rate and 7.1 month median survival in HER2-positive advance gastric cancer after failure of at least one prior chemotherapy [n = 27]. Concluded to be an active and safe treatment option [128]
	Afatinib	Irreversible pan-HER TKI	HER1, HER2, and HER4	43 % of patients with metasttic HER2-postive trastuzumab-refractory esophagogastric cancer treated with afatinib derived clinical benefit. Study currently ongoing, being expanded to include additional patients [n = 7] [129]
II/III	Pertuzumab	mAb	HER2[subdomain1], HER2 hetero dimerization	A phase II trial evaluating 2 different doses of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive advance gastric cancer is currently in progress [130]
				An international double-blinded, placebo-controlled, randomized phase III study, JACOB, is currently in progress evaluating pertuxumab (versus placebo) with trastuzumab and chemotherapy in patients with HER2-positive metastatic gastric or GEJ cancer (estimated enrollment:780) [131]
	Ado-trastuzumab	ADC	HER2 [subdomainIV]	Preclinical studies have found ado-trastuzumab emtansine to be more effective than trastuzumab in vitro as well as in vivo [132, 133]. A randomized, multicenter, adaptive Phase II/III study to evaluate the efficacy and safety of trastuzumab emtansine versus taxane (Docetaxel Or Paclitaxel) in patients with previously treated locally advanced or metastatic HER2-Positive gastric cancer is currently underway [134]

Table 3.1 (continued)

Clinical phase	Compound	Type of compound	Target	Study details +/- preliminary findings
III	Lapatinib	Reversible pan-HER TKI	HER1[EGRF] and HER2	LoGIC, a randomized, placebo-controlled, phase III study evaluating lapatinib in combination with chemotherapy [capecitabine plus oxaliplatin] in HER2-positive advanced or metastatic gastric, esophageal or GEJ adenocarcinoma found the addition of lapatinib did not improve clinical outcomes, with a hazard ratio (HR) of 0.91. However, certain subgroups, such as Asian patients and patients under 60 years old, showed improvement, HR = 0.68 and HR = 0.69, respectively (n = 545) [135]. TYTAN, randomized, placebo-controlled, phase II study evaluating labatinib in combination with paclitaxel as second line therapy in HER2-positve gastric cancer is currently underway. The interim safety analysis reported no significant issues (n = 107) [136]

of gastric carcinomas [72]. The HER2 gene is located on chromosome 17q21, and encodes a 185 kDa protein which belongs to the epidermal growth factor receptor (EGFR) family of transmembrane tyrosine kinase receptor proteins [73]. The EGFR family comprises four structurally-related members, HER1 (ErbB1 or EGFR), HER2 (ErbB2, c-erbB2 or Her2/neu), HER3 (ErbB3), and HER4 (ErbB4), which are all involved in activating downstream signaling pathways associated with cell proliferation, differentiation, migration, adhesion, survival, and angiogenesis [74].

HER2 is well recognized as a proto-oncogene, as its amplification results in overexpression of the HER2 RTK protein, which promotes cell proliferation and survival, properties promoting malignant transformation. In addition to being found on the cell membrane, HER2 receptors have also been localized to the cellular nucleus, functioning as transcription factors for proto-oncogenes such as cyclin D1 [75, 76].

HER2 was first identified as being overexpressed in gastric cancer in 1986; further investigations have reported its upregulation in as low as 4% to as high as 53% of gastric tumors [72, 77–79]. However, the exact timing of HER2 overexpression in the pathogenesis of gastric cancer is controversial. Several studies have demonstrated that HER2 upregulation is a late event during tumor progression, and hence describe it as a marker of advanced disease [80]. In contrast, other studies report HER2 overexpression in early stages as well as high concordance between HER2 expression in metastatic tissue and its associated primary tumor. This implicates HER2 overexpression as an early event with maintenance of HER2 expression being an important factor throughout the metastatic process [81, 82]. It has been well-established that HER2 overexpression varies across histological subtypes. HER2 overexpression is consistently found to be highest in the intestinal phenotype, followed by mixed, then diffuse phenotypes [78, 79, 81, 83–89]. In addition to histological subtype, anatomic localization of the primary tumor has been found to correlate with HER2 status. HER2 overexpression is more commonly found in tumors originating more proximally from the gastrooesophageal junction (GEJ) or stomach cardia, compared to those arising from the mid- and distal stomach [78, 79, 90]. In regards to the influence of patient demographics on HER2 status, a systematic review by Chua et al. found there to be no association between HER2 overexpression and age or gender [91]. Interestingly, a screening program part of a multicenter trial investigating treatment of HER2-positive gastric

cancer in 24 countries found that HER2 status varies geographically: Australia was found to have the highest percentage (33.2%) of HER2-positive gastric cancers and Taiwan the lowest (5.9%) [84].

HER2 overexpression has been clearly identified as a poor prognostic marker affiliated with decreased survival in breast cancer; however, its role in gastric cancer is less clear [92–94]. The relationship between HER2 expression in gastric cancer and prognosis was first studied in 1991, at that time it was identified as an unfavorable prognostic marker [95]. Over the past 2 decades, dozens of studies attempting to replicate the original finding that HER2 overexpression correlates with a favorable prognosis have yielded varying results. In 2012, two independently conducted systematic reviews concluded HER2 overexpression is associated with poorer prognosis [83, 91]. The review conducted by Chua and Merrett, which included 49 studies, totaling 11,337 patients, found median survival to be shorter in HER2-positive gastric cancers (21 months compared to 33 months). However, when assessing Overall Survival (OS) as a primary outcome measure, the majority of studies reported no significant difference in 20 of 35 studies which assessed OS. Additionally, there was no correlation between HER2 status and clinicopathologic characteristics such as tumor depth of invasion, TNM stage, presence of microvascular invasion or presence of perineural invasion. In contrast, Jorgensen and Hersom found that 71% of 42 studies, which included 12,749 patients, correlated HER2-positive status with poor survival and/or clinicopathological characteristics such as those mentioned above. More recent studies have identified HER2-positive status as a favorable prognostic factor in stage III and metastatic gastric cancers, however, on multivariate analysis HER2 was not identified as an independent prognostic factor [96, 97]. Additionally, a large surgical series found no correlation between HER2 status and OS in 829 stage II/III resected gastric cancer cases [98]. In summary, the role of HER2 in gastric cancer prognosis remains highly controversial and further investigation must be done before definitive conclusions can be drawn.

Despite controversies around prognostic properties of HER2, evidence supporting HER2 as an important therapeutic target in gastric cancer, especially when used in combination with conventional chemotherapy, is convincing. Treatment of HER2-positve breast cancer with trastuzumab, a fully humanized monoclonal antibody directed against the extracellular domain of HER2, has been proven to confer a survival advantage and its use is recognized as the standard of care [93, 99, 100]. Trastuzumab's antiproliferative effect is proposed to act through blockade of signaling pathways, downregulation of the HER2 protein, activation of apoptotic signals, and induction of antibody-depended cell medicated cytotoxicity [101, 102]. The 2010 Trastuzumab for Gastric Cancer (ToGA) phase III, open-label, randomized control trial, identified trastuzumab as the first molecular target shown to improve survival in metastatic gastric cancer when combined with platinum-5-fluorouracil chemotherapy, revolutionizing the treatment of HER2-positive gastric cancers. The addition of trastuzumab to chemotherapy was shown to significantly improve OS compared to chemotherapy alone (13.8 months compared to 11.1 months). An exploratory, post-hoc analysis that patients with HER2-positive tumors (IHC score of 2 with positive FISH or IHC score 3 independent of FISH score) were found to have a median OS of 16 months, compared to 10 months in the HER2-positve tumors that were FISH+ with an associated IHC score of 0 or 1 [103]. The results of the ToGA trial confirmed the safety and efficacy of the addition of trastuzumab to standard chemotherapy, prompting food and drug administration (FDA) approval for its application in combination with cisplatin and a fluoropyrimidine for the treatment of HER2-positive metastatic gastric or GEJ cancers [104]. Following the success of ToGA trial, a number of other HER2 targeted compounds have gone into clinical development, including several other monoclonal antibodies, an antibody-drug conjugate, and more recently, small molecule inhibitors (see Table 3.1; [78, 104–106]).

Molecular Signatures in Gastric Cancer

The clinical classification of GC as diffuse or intestinal does not currently dictate treatment [8, 19]. However, from the point of view of prognostication, these histologic classifications do predict different clinical courses [8, 19]. For example, different patterns of metastatic spread are observed in diffuse as opposed to intestinal type tumors [19]. Similarly, proximal gastric tumors carry a worse prognosis than more distal ones [19]. These findings imply differences at the genetic level [19]. Accordingly, contemporary studies demonstrate the existence of distinct molecular GC phenotypes, both between and within given histologic subtypes [13, 17, 19]. This permits classification along molecular lines, according to specific genetic changes. When considered within the context of known driver mutations, such classification may pave the way for more individualized, potentially effective treatments.

Molecular Signatures Within Histologic Subtypes

In the study by Shah et al., the authors sought to determine if genetic differences could be used to discriminate between histopathological subtypes of GC [19]. The authors categorized GC along three histologic subtypes: Proximal nondiffuse GC, diffuse GC, and distal nondiffuse GC. An analysis of gene up or downregulation between these groups revealed significant differences between them. Pathway analysis between GC subtypes and adjacent normal tissue revealed upregulation of metabolic pathways involved in lipid and carbohydrate metabolism in both proximal and distal non-diffuse type cancers. All subtypes demonstrated downregulation of known tumor suppressors including TP53. These results highlight the fact that genetic features underlie known histologic phenotypes and are responsible, at least in part, for their behavior. However, the authors did not identify clear differences between each GC subtype. This finding may reflect weaknesses inherent to histologic classification and is reflected in the more recent attempt to divide GC entirely along molecular lines [13, 17, 19].

Molecular Signatures Independent of Histologic Subtype

One problem with characterizing the molecular phenotype of GC along histologic lines is the assumption that all tumors belonging to a given group are the same at the genetic level. Current evidence suggests that this is not the case. For example, the study by Lei et al. demonstrates that genetically similar groups of GC can include both diffuse and intestinal type tumors [17]. By examining gene expression profiles, copy number alteration and DNA methylation patterns in 248 GC patients, the authors identified 3 GC subtypes: mesenchymal, proliferative, and metabolic [17].

The mesenchymal subtype demonstrated an overrepresentation of genes involved in focal adhesion, extracellular matrix receptor interactions, and cell adhesion compared to the other two subtypes. Mesenchymal tumors were predominantly of the diffuse type according to histologic classification (58.2%). However, significant proportions are of intestinal or mixed types (29.9 and 11.9% respectively) [17]. This tumor subtype was found to demonstrate cancer stem cell (CSC) like properties based on the observation of high CD44 expression and low CD24 expression [17]. This phenotype has been observed in CSC derived from prostate, breast, pancreatic, and gastric tumors [17]. Interestingly, CD44 overexpression has been associated with poor prognosis and reduced overall survival in GC [107]. CD44 is a cell surface receptor, which mediates interaction with ECM component, particularly HA [107].

CD24 is a GPI-anchored cell surface glycoprotein whose expression has been demonstrated in a variety of malignancies. It is thought to play a role in tumor growth, invasion and metastasis as well as in mediating sensitivity to certain chemotherapeutic agents [108]. In breast cancer, CD44 high/CD24 low tumors demonstrate stem cell-like properties, resistance to chemotherapeutic agents and may predispose patients to higher rates of relapse [108]. To date, such an association in GC remains unclear.

The proliferative subtype is enriched with regard to CNA compared to the mesenchymal and

metabolic subtypes [17]. In addition to genomic amplifications, this group exhibited a higher frequency of TP53 mutations compared to the other two. Additional characteristics of this group include a high degree of genomic instability, CpG hypomethylation, and amplification of known oncogenes, particularly CCNE1, MYC, ERBB2, and KRAS as well as deletions of PDE4D and PTPRD. As a consequence, the authors postulate excessive signaling via activation of E2F, MYC, and RAS pathways [17].

CCNE1 encodes cyclin E1, which functions in conjunction with Cdk 2 to regulate the G1/S phase transition [108]. While its specific role in driving GC carcinogenesis remains incompletely understood, its overexpression has been described in the context of other malignancies such as breast, and ovarian carcinomas [108, 109]. Its contribution to tumor progression is thought to be mediated by its ability to drive cell cycle progression [108, 109].

The MYC gene encodes the myc proto-oncogene, which functions as a regulator of proliferation, differentiation, and apoptosis [110]. Deregulated myc function alone can induce cellular transformation both in vitro and in vivo [110]. Aberrant myc function has been extensively demonstrated in gastric cancer ranging in frequency form 23.5–100 % of samples studied [110].

As previously stated, ERBB2 encodes the HER2 cell surface RTK whose activation leads to downstream signaling via both the PI3—Akt and p38-MAPK pathways [17, 22]. Aberrant KRAS signaling via the MAPK pathway has similarly been demonstrated in a significant proportion of GC patients, with KRAS representing an attractive potential therapeutic target in GC [25].

The gene products of PDE4D and PTPRD encode proteins involved in cAMP degradation and inhibition of RTK signal transduction [17, 111–113]. As such, they function as tumor suppressors with their inactivation contributing to unregulated and excessive signal transduction. In vitro inhibition of PDE4D has been shown to result in apoptosis and growth inhibition in a variety of human cancer cell lines including GC [111]. Similarly, PTPRD mutations have been demonstrated in a small proportion of gastric cancers and may be associated with tumor progression [112, 113].

Further examination if the proliferative subtype of GC demonstrates a preponderance of intestinal type tumors (73 %) compared to diffuse and mixed (17.3 and 9.1 % respectively) [17].

The final GC subtype was termed the metabolic subtype [17]. These tumors were found to bear genetic similarity to a premalignant gastric lesion known as spasmolytic polypeptide expressing metaplasia (SPEM) [17]. Like Intestinal metaplasia (IM), this lesion arises in the context of environmental insults such as H. *pylori* infection, and dietary nitrosamines. SPEM tends to localize to the body of the stomach and is associated with the loss of mature parietal and chief cells and a relative abundance of mucous producing neck and antral gland cells which express TFF2 (spasmolytic polypeptide), a secreted polypeptide normally expressed in the antrum and intestinal mucosa [114]. Roughly, equal proportions of diffuse and intestinal types characterized tumors of this type histologically (40.6 % diffuse, 53.6 % intestinal) [17]. Taken together, these results demonstrate an important heterogeneity in the molecular phenotype of gastric cancer that exhibits discordance with histologic classification [17].

Molecular Signatures in Gastric Cancer: Implications for Treatment

Interestingly, while no difference in survival was noted among the three subtypes identified by Lei et al., the molecular signatures predicted response to therapy [17]. Patients with tumors of the metabolic subtype were the most likely to demonstrate a survival benefit while receiving 5 FU-based chemotherapeutic regimens. This was attributed to the significantly lower levels of thymidylate synthase (TS) and dihydropyrimidine reductase (DHPR), which represent the target of 5FU and the enzyme responsible for its degradation respectively, in metabolic type tumors [17]. Along these lines, mesenchymal subtype cancers were postulated to demonstrate increased sensitivity to specific inhibitors of the PI3K-Akt-mTOR pathway. This was based on the observed activation of this pathway in mesenchymal subtype tumors

versus proliferative and metabolic subtypes. Accordingly, GC cell lines of the mesenchymal subtype demonstrate increased sensitivity to PI3-Akt-mTOR inhibitors [17].

The importance of genomic classification with respect to predicting response to treatment has been suggested by additional studies [13]. Recently, a study put forward by the Cancer Genome Atlas Group proposed the classification of GC into 4 groups entirely along molecular lines [13]. The authors identified four groups: EBV positive tumors, microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability. EBV positive tumors demonstrated a high degree of hypermethylation and frequent mutations in PIK3CA, suggesting a high degree of involvement of the PI3K-Akt pathway in such tumors. MSI tumors demonstrated silencing of genes associated with mismatch repair such as MLH1. In addition, frequently mutated genes in these tumors included current targeted therapy targets such as ERBB2. The genetically stable group demonstrated a high frequency of mutation within RHOA and CDH1, both the known driver mutations in GC, and the preponderance for diffuse type histology [13, 16]. Finally, tumors characterized by Chromosomal instability (CIN) demonstrated marked aneuploidy and frequent mutations in RTK. As in the previous study, no clear differences in the patient's survival could be identified between the 4 different groups [13]. However, a clear understanding of the characteristic genomic alteration associated with a given tumor subtype could suggest, which targeted therapies to apply and to whom [13]?

This approach to phenotypic characterization permits classification of gastric cancer types according to global changes in the gene expression as opposed to simply describing genetic abnormalities compared to nonneoplastic tissue. The implications of molecular characterization in this manner are that, more effective therapies can be administered based on a personalized approach to the diagnosis and management of GC [13, 17, 19].

Epigenetic Alterations in Gastric Cancer

In addition to mutations of the coding regions of genes, cellular expression profiles can be influenced by DNA modifications occurring within the noncoding regions [15, 16, 18, 25, 115]. Furthermore, such processes do not necessarily, directly alter the DNA sequences within a cell's genome. Rather, a number of structural chromatin modifications and alterations to mRNA transcripts can profoundly influence gene expression at the transcriptional and the translational levels [15, 16, 18, 25, 115]. Such alterations are said to be epigenetic and play an essential role in the normal tissue development [15, 115]. In addition, epigenetic processes have been shown to play an important role in the gastric tumorigenesis [15, 16, 18, 25, 115]. Among the epigenetic mechanisms describe thus far involved in the pathogenesis of GC are DNA methylation and the more recently described microRNA's [15, 16, 18, 25, 115].

Methylation

DNA methylation occurs at sites rich in the GC nucleotides termed as CpG islands (CGI) [15, 18]. These tend to cluster within the 5'UTR regions upstream of specific gene promoters [15]. Methylation within regions close to gene promoters, mediated by DNA methyltransferases, has a tendency to silence gene expression. Conversely, demethylation has a tendency to exert the opposite effect. In addition, methylation may occur outside the promoter region, sometimes within the coding sequences themselves. The effects associated with this type of methylation are more variable [15].

DNA methylation is the most extensively studied epigenetic change to take place in the context of GC to date [15]. Along these lines, a number of studies have highlighted genes whose transcription is modified by either hyper or hypo methylation. These include a large number of

genes involved in diverse fundamental cellular pathways including DNA repair, cell cycle progression, cellular adherence, invasion and migration, growth and differentiation, apoptosis, and transcriptional regulation [15].

As previously stated, hypermethylation within the promoter region has a tendency to reduce gene expression. Along these lines, a number of tumor suppressor genes are silenced in GC patients including MLH1, APC, and CDH1, involved in mismatch repair, *Wnt* signal transduction and cellular adhesion respectively [15–17, 25]. In addition to hypermethylation, a number of genes have been identified whose expression is upregulated by hypomethylation including genes such as CDX 1, which is involved in the development of intestinal metaplasia, MET, which encodes the HGF receptor, CLDN15, which belongs to the claudin family involved in tight junction formation, and TFF3, a transcription factor whose upregulation has previously been described in gastric cancer and which is expressed within normal columnar epithelium [15–17, 25, 116, 117]. These are but a few genes within a slew of others listed solely to highlight the diversity of cellular processes affected by the methylation status [15].

Given, the number and breadth of functions associated with proteins affected by DNA methylation in the GC, drawing any meaningful conclusions by simply listing them becomes prohibitive. In light of this fact, some studies have attempted to characterize methylation patterns in the GC patients within groups, or methylation signatures, in an attempt to draw conclusions regarding their biologic, and more importantly, their clinical significance [18]. Zouridis et al. characterized the DNA methylation profile in 203 primary GC samples and compared them to 94 matched control samples [18]. In so doing they identified distinct patterns of methylation associated with transcriptional repression or activation. In this manner, the authors demonstrated CGI methylator phenotypes (CIMP) in certain GC samples and identified DNA methylation inhibitors as a possible therapeutic avenue in CIMP tumors [18].

Methylation analysis of primary GC tumors demonstrated that the vast majority clustered into distinct groups, differentiating malignant tissue from benign gastric mucosa [18]. In addition, the majority of tumors [83 %] demonstrated hypermethylation. The remainder demonstrated marked and significant hypomethylation. In keeping with the observation that hypermethylation silences gene transcription, the authors identified that hypermethylation in CpG island (CGI) near to gene promoters resulted in gene silencing. They similarly demonstrated that the opposite also holds true, with hypomethylation near the promoter region correlating with gene upregulation. However, when hypermethylation within the coding regions of genes was identified, it was associated within genetic upregulation, with the converse being associated with genetic silencing. In addition, hypermethylation near promoter regions tended to cluster with hypomethylation within the coding regions and vice versa. Taken together, this date demonstrates a novel "tandem control" mechanism, whereby, methylation within the promoter region may interact with CpG methylation within genes themselves in order to exert global effects on transcriptional control [18]. Furthermore, tumors demonstrating long regions of hypomethylation were found to be significantly more prone to chromosomal breakage and accordingly demonstrated increased chromosomal instability compared to hypermethylated tumors [18]. Collectively, this data suggests that methylation patterns can exert profound effects on genetic control over great genetic distances [18].

The ability to categorize tumors according to methylation pattern has important implications [15, 18]. This is because methylation patterns are associated with neoplastic progression and patient outcome [15, 18]. For example, CIMP tumors tended to occur in younger patients, harboring poorly differentiated tumors. Such patients also demonstrated poorer outcomes independent of tumor stage compared to non-CIMP patients. Although CIMP tumors demonstrate downregulation of known tumor suppressors such as MLH1 and CDH1, their gene expression pattern did not permit their differentiation from non-CIMP tumors as readily as did their methylation pattern [18]. These finding led the authors to postulate that CIMP gastric cancers represent a distinct

tumor subset, not related to gene expression per se, but rather methylation pattern with profound implications with respect to clinical course [18].

In keeping with their previous observations, the authors sought to determine if ongoing methylation plays an important role in the tumorigenesis of CIMP neoplasms [18]. Treatment of CIMP cell lines with a DNA methyltransferase inhibitor resulted in diminished proliferation in vitro. Conversely, treatment of non-CIMP cell lines with a DNA methyltransferase inhibitor failed to reduce tumor cell growth. Furthermore, in vivo, significant reductions in tumor development were observed in CIMP positive tumors following concurrent treatment with a DNA methyltransferase inhibitor and cisplatin [18]. Thus, collectively this data indicates that GC may exhibit distinct methylation patterns that can predict a patient's clinical course and potential susceptibility to therapy [18]. Conceptually, these results imply that targeting specific mutations within coding regions may not encompass the entirety of where therapeutic modalities should be focused.

Micro RNA

Micro RNA's are a recently described class of RNA which play an extensive role in the post-transcriptional control of mRNA [14]. They are approximately 18–25 nucleotides in length and exert their effects via complementary binding with an mRNA molecule [14]. Such interactions can result in inhibition of translation or accelerated mRNA degradation [14]. Furthermore, a given mRNA can fall under the regulation of a single micro RNA or multiple different micro RNA. Similarly, a given micro RNA can interact with multiple mRNA transcripts [14, 115, 118]. These molecules play a significant role in post-transcriptional control and are thought to regulate up to 60 % of human genes at this level [14]. The preponderance of micro RNA is encoded within introns. However, they can localize within exons as well [14]. Transcriptional control of micro RNA is diverse, such that those located within introns fall under the transcriptional regulation of shared promoters [14]. Conversely, those located within exons are regulated by their own unique promoter [14]. As with all other genes, micro RNA transcription is subject to modification/disruption at the genetic level, as a result of genetic mutation, deletion, or amplification for example [14, 115, 118–120]. In addition, epigenetic processes such as DNA methylation can play a role [14, 115, 118–120]. However, globally, very little is known to date regarding the regulation of micro RNA.

As previously stated, micro RNA exert widespread regulatory effects within the cell, influencing basic cellular processes such as cell cycle progression, growth, and differentiation [14, 115, 118–120]. Accordingly, their dysregulation has been shown to play an important role in tumorigenesis [115]. With respect to GC, micro RNA molecules can function as either tumor suppressors or in an oncogenic capacity [115]. Along these lines both upregulation and downregulation of specific micro RNA molecules has been shown to exert pro-tumorigenic effects related to a number of fundamental processes including cell cycle progression, apoptosis, invasion, and metastasis [115, 118–120].

For example, the miR-106b-93-25 and miR222-221 micro RNA clusters are upregulated in GC. These micro RNA's target mRNA encoding the p57, p27, and p21 CDKI's. This results in their downregulation leading to cell cycle progression via the G1 to S phase transition [115].

Similarly, several micro RNA are upregulated and downregulated in GC which act in concert to inhibit apoptosis [115]. This includes upregulation of miR25, 130b, 150, and 222/221 and downregulation of miR375, 512-5p, 125-5p, 34, and 451. The net effect is increased inhibition of proapoptotic gene transcripts such as Bim, EGFR2, and RUNX3, and decreased inhibition of anti-apoptotic genes such as BCL2 [115].

These observations suggest that microRNA play a causal role in driving tumor progression in much the same way aberrant gene expression itself has been shown to do. Additional evidence supports this hypothesis [118–120]. For example, Li et al. demonstrated increased expression of miR 107 in gastric tumor tissue in a cohort of 50 GC patients compared to matched normal

controls [119]. The expression of miR-107 in these patients correlated strongly with DFS. Patients demonstrating high miR-107 expression exhibited a 5-year DFS of 24 % compared to 76 % in patients with low miR-107 expression [119]. In an attempt to demonstrate a causal link between miR-107 and metastasis, the authors performed a series of in vitro invasion and migration assays in GC cell lines known to express high levels of miR-107. Silencing miR-107 resulted in diminished invasive and migratory activity compared to wild-type cells. Tail vein injection of wild-type and miR-107 silenced GC cell lines mirrored the in vitro findings such that wild-type cells formed significantly more hepatic metastases that did silenced ones [119]. The oncogenic activity of miR-107 was attributed to its inhibitory effect on the tumor suppressor DICER 1, which encodes an endoribonuclease whose expression in metastatic GC is downregulated compared to normal tissue [119, 121]. In this manner, aberrant expression of microRNA can act to silence or activate critical tumor suppressors or oncogenes whose genetic integrity remains intact [119, 121].

Additional examples demonstrating the multifaceted, complex nature of aberrant gene expression in human GC have been put forward. For example, the tumor suppressor CDH1 (E-cadherin) is also subject to epigenetic posttranscriptional regulation by micro RNA [122]. Korpal et al. demonstrated repression of E-Cadherin translation via the downregulation of miR-200 family microRNAs. Restoration of miR-200 transcription rescues cellular E-cadherin expression. This upregulatory effect is mediated by the transcriptional inhibition of ZEB1 and ZEB2 transcription factors by mir-200. These transcription factors themselves mediate inhibitory effects on E-cadherin expression [122].

In contrast to the miR-200, miR-101 acts to promote E-cadherin function through its silencing effects on the EZH2 as demonstrated by Carvalho et al. [123]. This protein functions as a histone methyltransferase leading to chromatin remodeling, effectively inhibiting the transcription of a variety of genes including E-Cadherin [123]. Inhibition of EZH2 by miR-101 thus supports ongoing E-cadherin translation. Not surprisingly, the authors demonstrate evidence of miR-101 downregulation in patients with GC [123].

Another tumor suppressor, the Let-7f micro RNA is also downregulated in GC [120]. This micro RNA exerts its effects via the inhibition of a number of oncogenes including RAS and MYC. With respect to GC, Let-7f has been shown to inhibit the oncogene encoded by MYH-9 [120]. For example, inhibition of Let-7 in GC cell lines in vitro results in their increased migration and invasion. This effect persists in vivo where inhibition of Let-7 results in increased hepatic metastasis following systemic administration of Let-7 high or low expressing GC cells [120]. This effect is mediated by the inhibition of MYH-9 by Let -7. In keeping with this hypothesis, analysis of metastatic GC tissue demonstrates increased MYH-9 expression compared to primary tumor and surrounding normal tissue samples [120].

The data presented thus far represents a small fraction of what has been described with regards to the contribution of micro RNA to GC pathogenesis (Table 3.1; [14, 115, 118]). However, it serves to highlight the complex nature of this epigenetic mechanism of transcriptional regulation, which is redundant, and itself subject to complex regulation. Collectively, epigenetic mechanisms must be considered when interpreting data regarding the genetic profile of GC tumor samples. As the data highlighted above demonstrates, DNA methylation and microRNA expression can act in concert to exert profound effects on protein expression, even in the absence of genomic mutations afflicting tumor suppressors and oncogenes.

Conclusions

Gastric cancer remains a devastating disease worldwide. Despite advances in diagnosis and treatment, the mortality remains high. Current treatment algorithms are applied to patients based on disease stage at presentation without considering the heterogeneity of their underlying disease. This “one size fits all” approach may un-

derlie the disappointing results to date. However, recent efforts in the molecular characterization of GC have revealed numerous aberrations in tumor suppressors and oncogenes thought to drive the neoplastic process. Examination of these genes at the genetic and epigenetic levels has begun to reveal molecular phenotypes inherent to a given gastric neoplasm. This has permitted the classification of GC along molecular as opposed to histologic lines traditionally employed. As a consequence, an understanding of the predominant genes and pathways involved in a given neoplasm may become possible at the point of care. Such valuable information could allow for the rational application of targeted therapies based on the predominant genetic lesions associated with a given patients cancer.

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Pathology of Gastric Cancer

4

Laura H. Tang and Luke V. Selby

Abbreviations

GEJ	Gastroesophageal junction
EBV	Epstein–Barr Virus
FAP	Familial Adenomatous polyposis
HNPCC	Hereditary nonpolyposis colorectal cancer
MSI	Microsatellite instability
LGD	Low-grade dysplasia
HGD	High-grade dysplasia
WHO	World Health Association
EGC	Early Gastric Cancer

Introduction

Although the incidence of gastric cancer has steadily declined in past decades, gastric cancer remains the second leading cause of death from cancer worldwide. There is wide variation in the incidence of gastric carcinoma across different continents, with the highest rates in Asia, central Europe, and South America. In the USA, gastric cancer is the seventh most frequent cause of cancer-related death [1]. In the past several decades, changes in clinical practice have led to the diagnosis of a higher proportion of superficial and early-stage gastric cancers, which now represents almost 20 % of all newly diagnosed cancers in the USA and 50 % in Japan [2–5]. The anatomic distribution of gastric cancer is also changing, with the incidence of proximal gastric tumors rising and currently representing approximately 30 % of all gastric cancers [6, 7].

Epidemiologic, anatomic location, pathogenic factors, as well as molecular and genetic factors, and patterns of clinical practice all contribute to these demographic differences. This chapter intends to focus on the pathologic aspect of the disease and its implications in diagnosis and management of gastric carcinoma.

Pathogenesis of Gastric Carcinoma

Reflux

It has been well established that gastroesophageal junctional (GEJ) mucosa is frequently associated with acid reflux from the stomach. Patients with cardia cancer share similar characteristic risk factors with those for GEJ adenocarcinoma, such as age of onset and age distribution, a higher male-to-female ratio, morphologic phenotypes, and ethnic differences in disease distribution [8–12]. The association of cardia cancer with Barrett's esophagus and gastroesophageal reflux disease is a subject of debate, since the definition of true cardia carcinoma can be challenging

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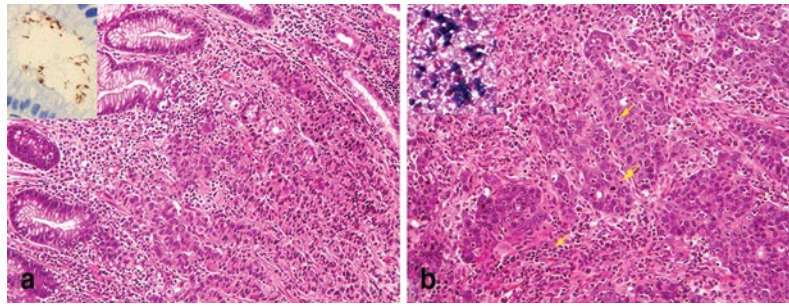

Fig. 4.1 *H. pylori* and Epstein–Barr virus infection associated gastric adenocarcinoma. **a** An adenocarcinoma arises in association with active chronic gastritis with *H. pylori* organisms identified on immunohistochemical stain (*insert*). **b** A poorly differentiated carcinoma with intense intraepithelial and stromal lymphocytic infiltration (*arrow*) and EBV genome is identified by in situ hybridization (*insert*)

when the tumor is large and involves the gastroesophageal junction [12]. As many as 70% of the cardia carcinomas have a component of intestinal metaplasia, an early pathologic process similar to that observed in Barrett's esophagus associated adenocarcinoma at the GEJ.

Interestingly, prior gastric surgery in male patients, particularly subtotal gastrectomy with Billroth II reconstruction is associated with an increased risk for the subsequent development of remnant gastric cancer, probably due to enterogastric reflux of bile and pancreatic secretions [13–16].

Infection

Helicobacter pylori infection is a major environmental cause of gastric cancer. Long-standing *H. pylori* infection induces chronic gastritis, which results in mucosal atrophy and intestinal metaplasia [17, 18] (Fig. 4.1a). There is a 4–9 fold increased risk of gastric neoplastic lesions among patients with *H. pylori* infection, particularly if infection began in early childhood [19–21]. Certain aspects of *H. pylori* virulence have been associated with risk of gastric cancer. In particular, the strains which are positive for cytotoxin-associated gene A (CagA) produce higher levels of interleukin 8 which elicit more intense inflammation. These strains are associated with an increased risk of gastric carcinoma [22]. However, gastric cancer does not develop in most individuals who have *H. pylori* infection, and other environmental and host factors are presumed to be important in the pathogenesis of this disease [23, 24].

Epstein–Barr virus (EBV) has long been recognized as a distinct pathogenic cause of gastric carcinoma [25, 26]. EBV is detected in about 10% of the gastric carcinoma cases (Fig. 4.1b). All tumor cells in EBV-associated gastric carcinoma harbor the clonal EBV genome. Gastric carcinoma associated with EBV occurs predominately in men and in younger-aged individuals. These carcinomas exhibit a unique histologic phenotype, genetic/epigenetic genotype, and distinct clinicopathological features [25, 27–29].

Autoimmune Gastritis

Autoimmune gastritis arises secondary to an immune-mediated destruction of parietal cells (pernicious anemia), is confined to the body and fundus of the stomach, and is characteristically associated with neuroendocrine cell (enterochromaffin-like cell) hyperplasia and neoplasia (Fig. 4.2). In patients with autoimmune associated atrophic gastritis, most adenocarcinomas are of the intestinal type and the risk of gastric cancer increases at least three fold [30]. In contrast, gastric type-1 neuroendocrine (carcinoid) tumors arising in autoimmune atrophic gastritis are relatively indolent in their behavior [31].

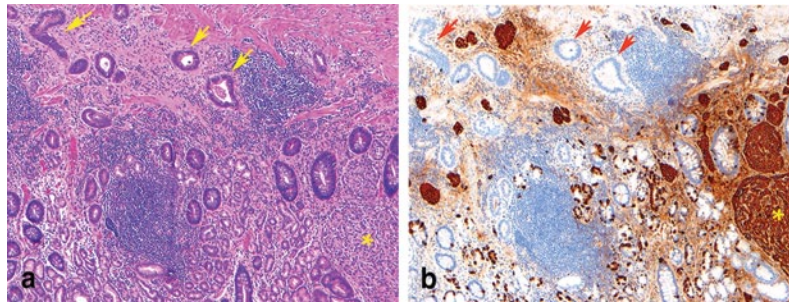

Fig. 4.2 Type-I gastric neuroendocrine tumor and the coexisting adenocarcinoma. Histopathology of a neuroendocrine tumor (*star*) exhibits a nested pattern (**a**) and the immunoreactivity for chromogranin (**b**) is present in the background of hyperplastic neuroendocrine cells and neuroendocrine tumor. A well differentiated and gland-forming adenocarcinoma (*arrow*) invades the muscularis mucosa and infiltrates the submucosa

Gene-Dietary Interaction

Environmental factors in addition to *H*. pylori infection, including cigarette smoking and diet, play an important role in gastric carcinogenesis [32]. Foods that are salted, smoked, pickled, and preserved foods rich in salt, nitrites, or preformed N-nitroso compounds are associated with an increased risk of gastric cancer [33].

Genetic polymorphisms may also contribute to the etiology of gastric cancer by altering the activity of enzymes that are involved in multiple molecular processes, such as DNA synthesis and repair, carcinogen metabolism, the inflammatory response, and tumor suppression [34]. Individuals who carry high-risk genetic variants and high-risk diets have an increased risk of gastric cancer compared with those who do not carry high-risk genetic variants or those with high-risk genetic variants but low-risk diets. Distinctive dietary patterns and regional variations in genetic polymorphisms may explain regional variations in gastric cancer incidence [35–37].

Hereditary

Approximately 10% of all gastric cancers are familial. Germline mutations in the E-cadherin CDH1 gene account for 30–40% of the rare syndrome known as hereditary diffuse gastric cancer, and gastric cancers also occur less frequently as a component of other hereditary cancer syndromes [38].

Familial Diffuse Gastric Carcinoma

Germline mutations in CDH1 are the molecular basis for familial gastric cancer syndrome [39–42] (Fig. 4.3a). Initially identified in three Maori families in New Zealand, at least 100 families have been reported to carry the CDH1 germline mutation [43]. Given the relatively high penetrance disease (70–80%) [44], a lifetime risk of developing gastric cancer of approximately 67% in men and 83% in women [45], prophylactic total gastrectomy is often considered after a familial diagnosis of a CDH1 mutation [46]

Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Syndrome

After endometrial carcinoma, gastric carcinoma is the second most common extra-colonic cancer in patients with hereditary nonpolyposis colorectal cancer (HNPCC) (Fig. 4.3b). There is a four-fold relative risk of developing gastric cancer in HNPCC patients, with the risk predominantly in younger patients (11.3-fold in the 30s and 5.5-fold in the 40s). Additionally, the relative risk is greater in mutation carrier families than noncarrier families (3.2-fold versus 1.6-fold). The overall lifetime risk of developing gastric cancer is 10% for patients of Western ancestry and 30% for patients of Asian ancestry [54–57], and microsatellite instability (MSI) phenotype is noted in 65% of these cases.

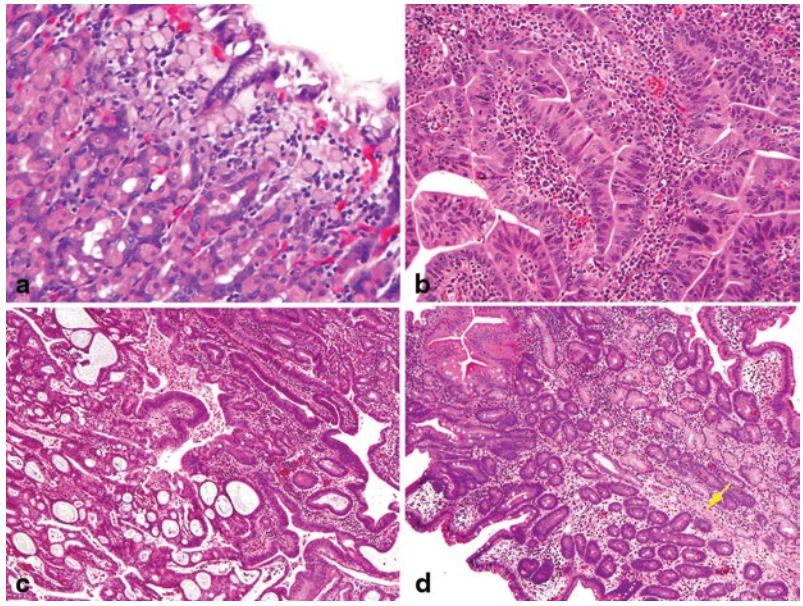

Fig. 4.3 Hereditary condition associated gastric neoplasms. **a** Early hereditary diffuse gastric carcinoma with signet ring cell morphology is present in the superficial lamina propria. **b** HNPCC (Lynch syndrome) associated intestinal type gastric adenocarcinoma exhibits increased intraepithelial and stromal lymphocytes. **c** An FAP associated adenocarcinoma (*left*) arises in a fundic gland polyp with dysplasia (*upper right*). **d** Gastric Peutz–Jeghers polyp is composed of irregular and architecturally distorted proliferation of foveolar glands with increased inflammation in the lamina propria and smooth muscle proliferation (*arrow*)

Familial Adenomatous Polyposis Coli (FAP)

Patients with familial adenomatous polyposis coli (FAP) also develop multiple gastric fundic gland polyps, which can undergo neoplastic transformation as a result of somatic mutations of the adenomatous polyposis coli (APC) gene [47] (Fig. 4.3c). However, in contrast to the development colon adenocarcinoma from adenomatous polyps in FAP patients, the development of gastric carcinoma in fundic gland polyps is rare [48–51]. Interestingly, there is a higher risk of neoplastic transformation in the stomach of Asian FAP patients as compared to Western FAP patients [52, 53].

Li–Fraumeni Syndrome

Germline mutations of the TP53 gene are present in 50–70% of the patients with Li–Fraumeni syndrome.The most common neoplasms in patients with Li–Fraumeni syndrome are soft tissue sarcoma, breast cancer, and brain tumors. While gastrointestinal tract tumors account for less than 10% of all Li–Fraumeni syndrome associated neoplasms, gastric carcinomas (which may be multiple) represent more than 50% of the gastrointestinal tumors in patients with Li–Fraumeni [58, 59].

Peutz–Jeghers Syndrome

Mutation of the serine/threonine–protein kinase 11 (STK11) gene, located on chromosome 19p13.3, is responsible for Peutz–Jeghers syndrome [60]. Characteristic gastrointestinal hamartomatous polyps develop (Fig. 4.3d), and these patients have an increased risk of gastric cancer, although the exact degree of risk is a subject of debate [61, 62].

Gastric Hyperplastic Polyposis

Gastric hyperplastic polyposis is an inherited autosomal dominant syndrome characterized by the presence of hyperplastic gastric polyposis, severe psoriasis, and an increased incidence of gastric cancer of the diffuse type [63, 64].

Precursors of Gastric Carcinoma

The well-defined chronic inflammation-intestinal metaplasia-glandular dysplasia—cancer sequence typically precedes the development of most intestinal type gastric adenocarcinomas [65]. While intestinal metaplasia proceeded by epithelial dysplasia (type I) may be present as a polypoid lesion and resemble a colonic adenoma, it is genetically distinct from the typical tubular adenoma in the colon. In contrast to adenoma-carcinoma sequence in colonic adenocarcinoma (which is usually associated with an intrinsic genetic abnormality in the APC molecular pathway) the progression of intestinal dysplasia to gastric adenocarcinoma occurs with a stepwise accumulation of multiple genetic abnormalities. True *de novo* gastric adenomas are rare outside the setting of FAP, in which gastric fundic gland polyps progress to epithelial dysplasia secondary to inherent APC gene abnormality. A less common histologic variant of dysplasia is gastric foveolar (type II) dysplasia with a gastric mucin phenotype [66]. The significance of these subtypes remains controversial and phenotyping of gastric dysplasia is not recommended at this time.

The natural history of gastric dysplasia depends on its grade, extent of dysplasia, and surface appearance (polypoid versus flat or depressed). Dysplasia is graded based on cytologic and ar-

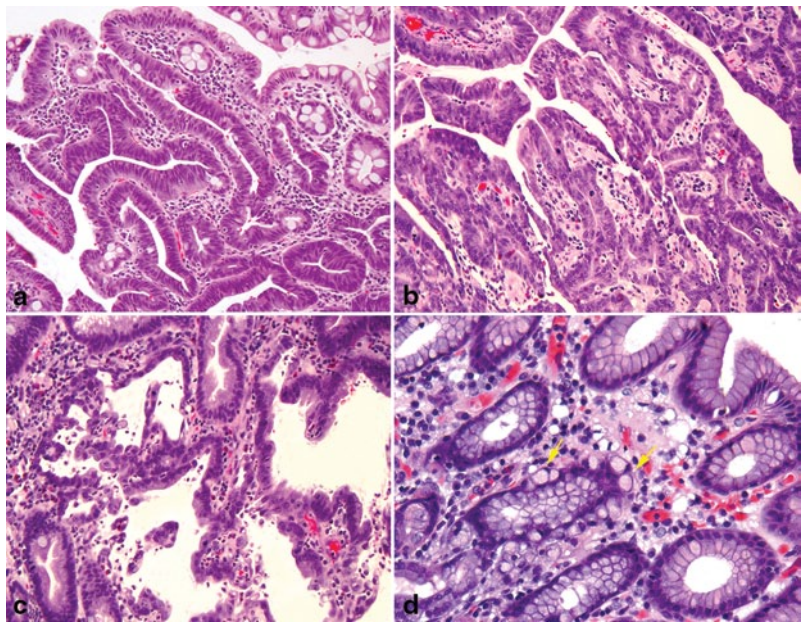

Fig. 4.4 Precursors of gastric adenocarcinoma. **a** Long standing chronic gastritis is followed by intestinal metaplasia (*upper right*) and low-grade glandular dysplasia which is demonstrated by nuclear elongation and pseudostratification. **b** High-grade dysplasia exhibits loss of cellular polarity of the epithelium with glandular crowding and architectural alteration which approaches the criteria of early carcinoma. **c** Even in the absence of invasion into the stroma, early adenocarcinoma proceeded from high-grade dysplasia is demonstrated by expansile crypt growth with cribriform complexity. **d** In situ signet ring cell carcinoma is present within the basal membrane with hyperchromatic and depolarized nuclei and pagetoid spread of signet ring cells (*arrow*)

chitectural features as either low grade (LGD) or high grade (HGD) (Fig. 4.4a, b). Low-grade dysplasia diagnosed on endoscopic biopsies has been shown to regress in 38–75% of the cases, to persist in 19–50%, and to progress to HGD in 0–9% of the cases [67]. The best independent predictors of progression to adenocarcinoma are lesions greater than 2 cm and a depressed configuration on endoscopic examination [68].

High-grade dysplasia regresses in only 0–16% of the cases, persists in 14–58%, and progresses in 10–100% to adenocarcinoma (Fig. 4.4c) [67]. Given the high probability of progression to adenocarcinoma, a lesion diagnosed as HGD on endoscopic biopsy should be considered for endoscopic mucosal resection if feasible or surgical resection if HGD is present as multifocal lesions or if endoscopic mucosal resection is not technically feasible.

The precursor of diffuse gastric carcinoma is thought to originate from oxyntic gland tubule neck (or globoid) dysplasia [69] in situ signet ring cell carcinoma. This corresponds to the presence of signet ring cells within the basal membrane, generally with hyperchromatic and depolarized nuclei and pagetoid spread of signet ring cells below the preserved epithelium of glands/foveolae (Fig. 4.4d) [70].

Pathologic Classification

Tumor Location

The location of gastric adenocarcinoma may, to some extent, reflect the pathogenesis of the disease. For example, intestinal type adenocarcinoma in the proximal stomach may be associated with a reflux etiology (Fig. 4.5a), while intestinal type adenocarcinoma in the distal stomach is more likely related with *H. Pylori* infection associated pathogenesis (Fig. 4.5b). Diffuse type gastric cancer is more commonly located in the middle third and body of the stomach (Fig. 4.5c), while remnant cancer is invariably located in the gastric mucosa at duodenogastric anastomosis (Fig. 4.5d). Determination of a precise tumor location can be challenging and even subjective, especially when the lesion is large and straddles multiple anatomical sites within the stomach. Nevertheless, documentation of the relative location of the tumor is important for the elucidation of potential pathogenesis and classification of the disease, as well as for the evaluation of the extent of the disease and the resection margin status.

Gross Pattern

The gross configuration of advanced gastric cancer can be classified using Borrmann classification, which designates gastric carcinomas into four distinct types[71]: polypoid (type I), fungating (type II), ulcerating (type III), and diffusely infiltrating (type IV). Diffusely infiltrating is also referred to as linitis plastica when it involves nearly the entire stomach and it is consistently associated with the diffuse histologic subtype. In contrast, types I, II, and III are associated with other histologic subtypes. Type II, the most common subtype, represents 36% of all gastric carcinomas and is frequently detected on the lesser curvature of the antrum. Types I and III each represent 25% of all advanced gastric carcinomas, and they are more common in the corpus, usually on the greater curvature.

Histologic Classification

Gastric cancer represents a heterogeneous group of tumors with diverse pathogenesis, morphologic features, and molecular backgrounds. While recent genomic analysis has identified several subtypes of gastric adenocarcinoma by their generic signatures [29], histopathologic classification remains critical for a number of clinical assessments of the disease and serves as the basis for the molecular classification of the disease [72, 73]. Several systems have been proposed to aid in the classification of gastric adenocarcinoma based on the microscopic futures of the tumor [74–76]. The two most commonly used histologic classifications are the Laurén classification and the World Health Organization (WHO) systems [77, 78]; significant correlation is seen between these two schemes [79].

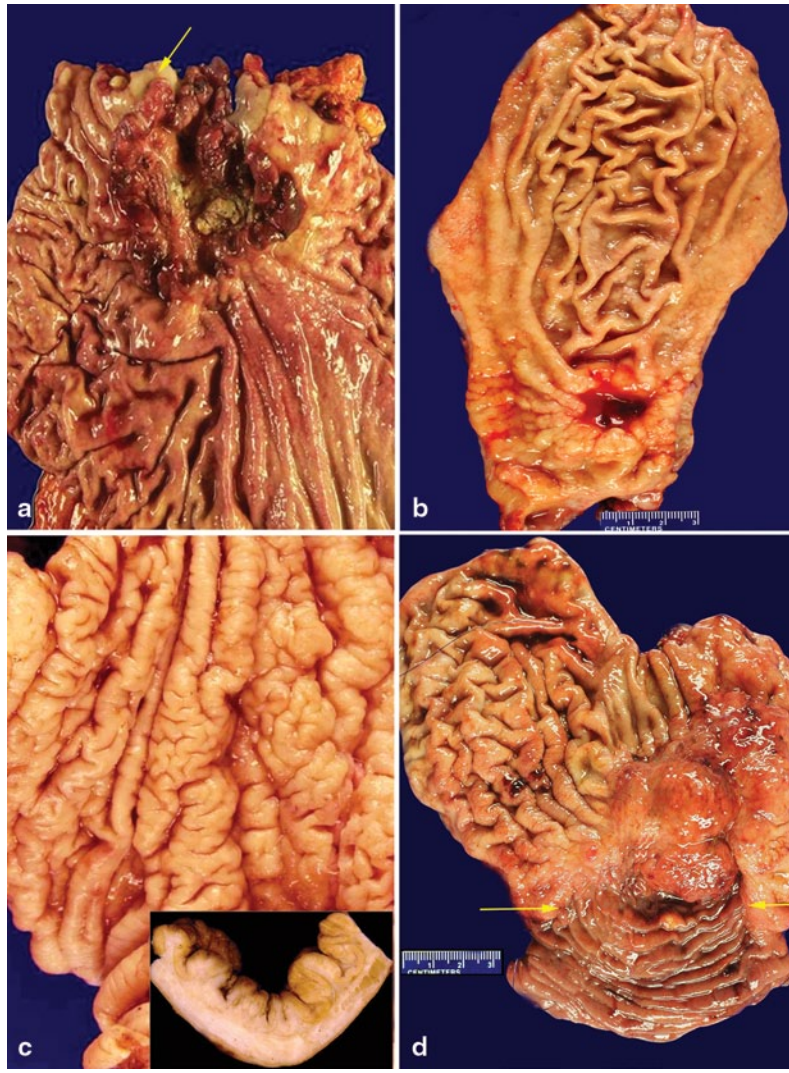

Fig. 4.5 Gross pathology of gastric adenocarcinoma. **a** A proximally located gastric adenocarcinoma with minimal extension into the squamous mucosa (*arrows*) of the esophagus. **b** An ulcerated intestinal carcinoma is located in the distal stomach. **c** A diffuse type adenocarcinoma is located in the body of the stomach with intact mucosa but rigid mucosal fold. A cross section of the mucosa reveals thickened gastric wall secondary to diffuse infiltration by tumor cells. **d** A remnant gastric cacumina is located in the gastric mucosa near the anastomotic line (*arrows*)

The Laurén classification separates gastric adenocarcinomas into two primary subtypes: intestinal and diffuse, and tumors exhibiting features of both the intestinal and diffuse types are designated as mixed-type adenocarcinoma (Fig. 4.6a, b, c, d). The intestinal type is characterized by the formation of glands exhibiting various degrees of differentiation either with or without extracellular mucin production (Fig. 4.6a). The diffuse type of gastric adenocarcinoma is composed of poorly cohesive cells without gland formation (Fig. 4.6b, c). This type of tumor often contains cells with intracytoplasmic mucin, known as "signet ring cells" (Fig. 4.6c), although this term has been synonymously used for diffuse cancer even in the absence of intracytoplasmic mucin (Fig. 4.6c). In addition to their distinct morphologic characteristic, the intestinal and the diffuse

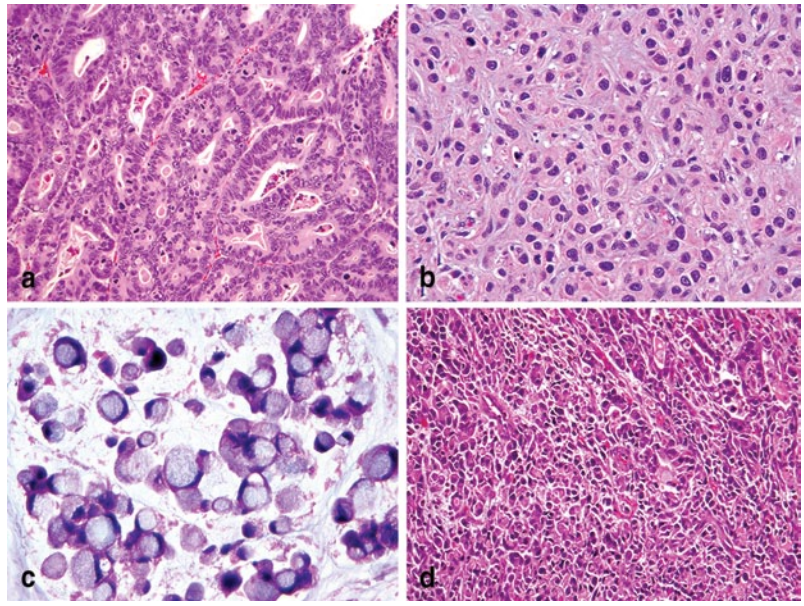

Fig. 4.6 Lauren's histopathology classification of Gastric Carcinoma. **a** Intestinal type adenocarcinoma with well-formed glandular and tubular architecture. **b** Poorly differentiated diffuse type adenocarcinoma. **c** Diffuse type adenocarcinoma with intracellular mucin and signet ring cell features. **d** Lauren's mixed type adenocarcinoma with a small component of poorly differentiated intestinal phenotype (*upper right*) and a poorly differentiated diffuse/poorly cohesive carcinoma with focal signet ring cell features (*left*)

subtypes of gastric adenocarcinoma also have different clinicopathologic features (Table 4.1).

While the basis for the initial Laurén classification was exclusively morphologic characteristics, accumulative knowledge in the epidemiology and pathogenesis of gastric carcinoma has indicated that this classification system is also valuable in defining molecular subtypes of gastric cancer [72, 73]. In the absence of significant chronic gastritis, intestinal metaplasia, or dysplasia, pure diffuse type of gastric cancer probably represents either a hereditary or sporadic ideology. However, significant components of diffuse or poorly cohesive carcinoma can be seen in mixed adenocarcinoma with inflammation-metaplasia-dysplasia-carcinoma precursors, often complicating molecular analysis of the tumor.

In 2010 the WHO revised its morphologic classification to reflect the patterns exhibited throughout the gastrointestinal (GI) tract [78]. This classification recognizes five major types of gastric adenocarcinoma based on the predominant histologic growth pattern: (1) papillary, (2) tubular, (3) mucinous (tumors with

Table 4.1 Clinical and pathologic features of Laurén subtype gastric adenocarcinoma

	Intestinal type	Diffuse type
Onset age	Older than 50 year	Younger than 50 years
Gender	Male > Female	Male = Female
Geographic distribution	Asia (China Japan, Korea)	Anywhere
Precursor lesion	Intestinal metaplasia/dysplasia	Signet ring cell carcinoma in situ
Common location	Antrum or cardia	Body
Borrmann classification	Type I, II, III	Type IV
Genetic association	HNPCC, AFP	Hereditary diffuse gastric cancer, hyperplastic polyposis

Table 4.2 WHO classification of carcinoma of the stomach [99]

Tumor type	Histologic features
Adenocarcinoma	
Papillary adenocarcinoma	Exophytic with elongated frond-like tumor extensions with fibrovascular cores; usually better differentiated and low grade
Tubular adenocarcinoma	Dilated or slit-like branching tubules; usually low, although poorly differentiated variants are not uncommon
Mucinous adenocarcinoma	Contains more than 50% extracellular mucin pools. May contain scattered signet-ring cells more commonly seen in proximal/cardia location
Poorly cohesive carcinomas, including diffuse and signet-ring cell carcinoma and other variants	Tumor cells infiltrate as isolated single cells or small aggregates. The carcinoma is predominantly composed of signet-ring cells containing a clear droplet of cytoplasmic mucin displacing the nucleus. Other variants of poorly cohesive carcinoma may resemble mononuclear inflammatory cells
Mixed carcinoma	Mixture of morphologically identifiable components such as tubular, papillary, and poorly cohesive patterns
Adenosquamous carcinoma	Mixture of glandular and squamous neoplastic components; the squamous component should comprise at least 25% of the tumor volume
Carcinoma with lymphoid stroma (medullary carcinoma)	Poorly developed glandular structures associated with a prominent lymphoid infiltrate in the stroma. Associated with EBV infection or HNPCC-associated carcinoma and may have a favorable prognosis
Hepatoid adenocarcinoma	Large polygonal eosinophilic tumor cells resembling hepatocytes; may express alpha-fetoprotein
Squamous cell carcinoma	Both Keratinizing and nonkeratinizing forms are encountered
Undifferentiated carcinoma	High-grade carcinoma that cannot be further classified as adenocarcinoma, squamous cell carcinoma, or other recognized variants
Neuroendocrine carcinoma	Poorly differentiated high-grade carcinoma with diffuse or focal synaptophysin chromogranin-A expression. These tumors exhibit a high mitotic rate (>20 per 10 high power field, and Ki67 is usually >50%) marked nuclear atypia, and may have focal necrosis
Large cell neuroendocrine carcinoma	Tumor cells are large, with moderate amount of cytoplasm, and may contain prominent nucleoli
Small cell neuroendocrine carcinoma	Tumor cells are small, with finely granular chromatin and indistinct nucleoli
Mixed adenoneuroendocrine carcinoma	Composed of both gland-forming and neuroendocrine malignant elements, with at least 30% of each component. Identification of scattered neuroendocrine cells in adenocarcinomas by immunohistochemistry does not qualify as mixed carcinoma

mucinous pools exceeding 50% of the tumor), (4) poorly cohesive (including signet ring cell carcinoma and other variants), and (5) mixed adenocarcinomas (Table 4.2). Uncommon variants of gastric carcinomas include the squamous cell, adenosquamous, hepatoid (Fig. 4.7a), micropapillary, carcinoma with lymphoid stroma (medullary carcinoma) (Fig. 4.7b), carcinoma with pancreatic acinar differentiation (Fig. 4.7c), choriocarcinoma [80, 81], undifferentiated subtypes (Fig. 4.7d), carcinoma with sarcomatous differentiation (Fig. 4.7e), high grade neuroendocrine carcinoma of small cell or large cell subtype (Fig. 4.7f), and carcinoma arising in gastric heterotopia in the esophagus (gastric inlet) or pancreatic heterotopia. The so called medullary carcinoma usually has an expansile growth pattern with intratumoral and peritumoral lymphocytic infiltration; this tumor phenotype is commonly associated with either EBV or microsatellite instability associated gastric carcinoma. The relevant clinical implication when encountering these rare subtypes of gastric carcinoma is that a metastasis should be excluded before entertaining a diagnosis of primary gastric carcinoma. In addition, any histologic subtype of gastric carcinoma, when poorly differentiated, can present with either partial or entirely sarcomatous features (sarcomatoid carcinoma) (Fig. 4.7e), which

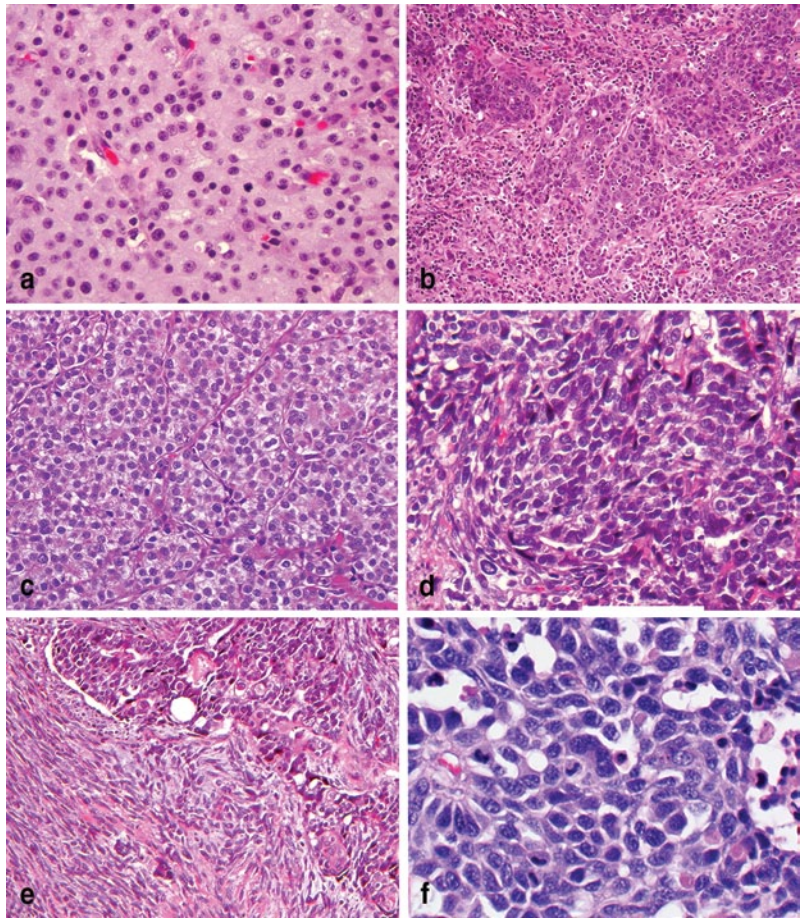

Fig. 4.7 Uncommon histopathologic variants of gastric adenocarcinoma. **a** Adenocarcinoma with hepatoid features. **b** Medullary adenocarcinoma with markedly increased intraepithelial and stroma lymphocytes (*small blue cells*). **c** Adenocarcinoma with prominent pancreatic acinar differentiation. **d** Undifferentiated carcinoma. **e** Undifferentiated carcinoma (*upper right*) with sarcomatous differentiated (*low left*). **f** High grade neuroendocrine carcinoma, small cell type

is not uncommon in the upper gastrointestinal tract or the pancreaticobiliary carcinoma.

Diagnostic Issues

Primary Versus Metastasis

The pathologic diagnosis of gastric adenocarcinoma, particularly a poorly differentiated and nonintestinal subtype, can be challenging with a biopsy specimen. While stomach is not a common site for metastasis, a number of epithelioid neoplasms can metastasize to the gastric mucosa and the differential diagnosis between a primary gastric carcinoma and a metastasis may be difficult in small biopsies [82, 83]. Patients may be asymptomatic, present with a bleeding ulcer mimicking a primary gastric carcinoma (39 % of the cases), or with a submucosal tumor (51 % of the cases).

The most commonly observed error in the diagnosis of diffuse signet ring cell carcinoma occurs with metastatic lobular breast carcinoma, which has a propensity to metastasize and colonize the gastrointestinal tract as well as other

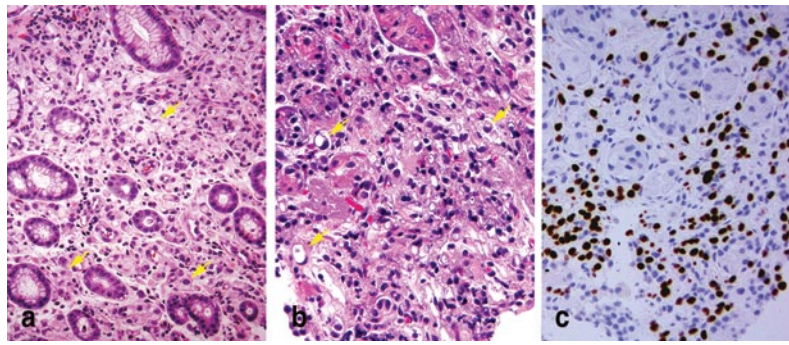

Fig. 4.8 Differential diagnosis of diffuse carcinoma in gastric biopsies. Primary diffuse gastric carcinoma (**a**) and metastatic breast lobular carcinoma to the stomach (**b**) share morphologic features (*Arrow*) and the distinction between them may sometimes be impossible. An immunostain for estrogen receptor is usually positive in classic lobular carcinoma (**c**)

hollow organs such as the uterus and the urinary bladder. Primary gastric diffuse signet ring cell carcinoma and lobular breast carcinoma share similar morphologic features and sometimes, the two neoplasms can be indistinguishable on the morphologic basis alone (Fig. 4.8a, b). Immunohistochemical studies can be helpful, since classic lobular breast carcinoma is usually immunoreactive to estrogen receptor (ER) (Fig. 4.8c), cytokeratin-7 (CK7), and mammaglobin; and a gastric primary carcinoma is immunoreactive for both CK7 and CK20, and should be negative for ER and mammaglobin.

Most importantly, a clinical history, even in the remote past, of breast carcinoma should prompt the appropriate work up to exclude a metastasis before the diagnosis of primary gastric diffuse signet ring cell carcinoma. Female patients with hereditary CDH1 mutation are at risk of developing both diffuse type gastric adenocarcinoma and lobular breast carcinoma, although the reported incidence of the latter is lower [45].

Gastrointestinal stromal tumor (GIST) can occur at any site of the GI tract; the stomach is one of the most common locations. When a GIST has epithelioid morphology, it can be difficult to distinguish from a poorly differentiated primary gastric carcinoma. Although subtle morphologic details may suggest the diagnosis of a GIST, such as intercellular myxoid stroma (Fig. 4.9a), a lack of cytokeratins immunoreactivity and positive reactivity to c-kit (CD117) confirms a diagnosis of GIST (Fig. 4.9b).

Other poorly differentiated malignant epithelial or epithelioid tumors, including seminoma (Fig. 4.9c), melanoma (Fig. 4.9d), and renal cell carcinoma, can metastasize to the stomach. Therefore, a poorly differentiated neoplasm in a gastric biopsy requires a thorough clinical and pathologic evacuation to exclude the possibility of a metastasis before the establishment of a primary gastric cancer. Among metastatic glandular/tubular carcinomas, pulmonary and pancreatic origins are more common than other primaries.

Biopsy Diagnosis of Early Gastric Cancer

Adenocarcinoma confined to the gastric mucosa (pathologic stage pT1a) or submucosa (pT1b) is defined as early gastric cancer (EGC) [7], and represents an early stage in tumor development. In Western series, EGC represents 15–20% of the newly diagnosed gastric cancers, whereas in Japan it accounts for more than 50% of the cases [2–5]. A higher prevalence of gastric cancer, more liberal use of upper endoscopy and chromoendoscopy, and differences in diagnostic criteria may explain the differences between Western and Japanese studies.

Most EGCs are typically located on the lesser curvature, around the angularis, and majority of them are well differentiated tubular or papillary

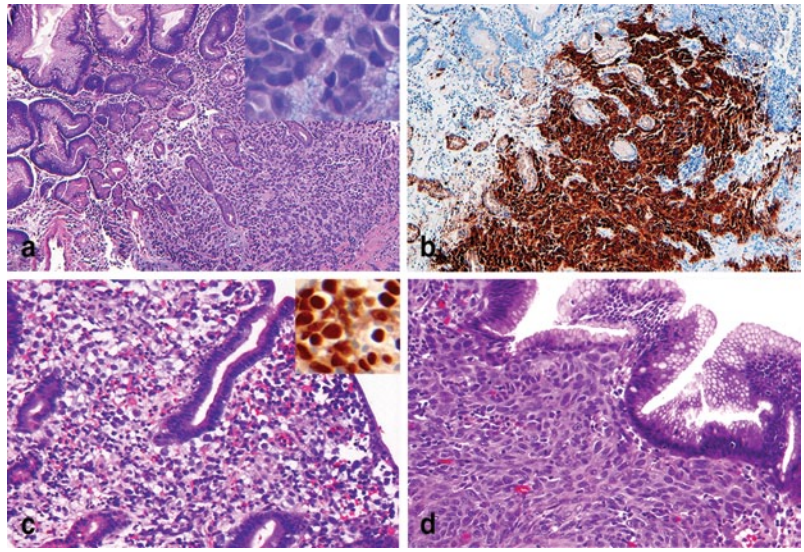

Fig. 4.9 Differential diagnosis of poorly differentiated epithelioid neoplasms in gastric biopsies. **a** Epithelioid gastrointestinal stromal tumor (GIST) involves gastric mucosa; the tumor cells exhibit intercellular myxoid stromal (*insert*) which is a subtle feature of GIST. **b** An immunostain of c-KIT (CD117) can confirm the diagnosis of GIST. **c** Metastatic seminoma involving gastric mucosa and an immunostain of octamer-binding transcription factor 4 (OCT4) (*insert*) is usually positive in tumor cells. **d** Metastatic melanoma involving gastric mucosa

variants [7]. These features create a challenging differential diagnosis between high-grade glandular dysplasia/carcinoma in situ (pTis) (Fig. 4.10a), and minimally invasive carcinoma (pT1a). The latter may present as either (1) individual cribriform glands with an associated expansile growth pattern (Fig. 4.10b) or (2) with nominal tumor invasion in the lamina propria (Fig. 4.10c); in both histologic prototypes, the tumor has progressed beyond the level of glandular dysplasia and met the diagnostic criteria of superficial gastric adenocarcinoma. When carcinoma invades through the muscularis mucosa, the tumor is staged as pT1b (Fig. 4.10d). Diffuse-type EGCs tend to exhibit greater width and depths of invasion and thus are less challenging to diagnose.

In some situations, well differentiated tubular or papillary adenocarcinomas may be present as detached fragments in a superficial biopsy. In the absence of stroma in a biopsy, the distinction between glandular dysplasia (pTis), genuine superficial carcinoma (pT1a), or invasive carcinoma in an exophytic mass is difficult to establish on the basis of microscopic features (Fig. 4.11). Nevertheless, correlations of endoscopic impressions and histologic findings can facilitate the accurate diagnosis.

Intraoperative Margin Assessment

Resection margins are among the strongest predictors of cancer-related mortality for gastric adenocarcinoma. An intraoperative consultation with a pathologist, including a frozen section of the specimen to microscopically assess the margin status, offers an opportunity to modify surgical management with the goal of achieving an R0 resection. The frozen section interpretation of the proximal margin deserves special attention since this is where most errors occur. In one study, the estimated overall diagnostic accuracy of frozen section at the proximal margin was 93 %, with a sensitivity of 67 %, a specificity of 100 %, a positive predictive value of 100 %, and a negative predictive value of 91 % [84]. Importantly, diffuse signet ring cell cancer constitute > 83 % of the false-negative readings.

When assessing the margin status, the specimen is opened to examine the location of the

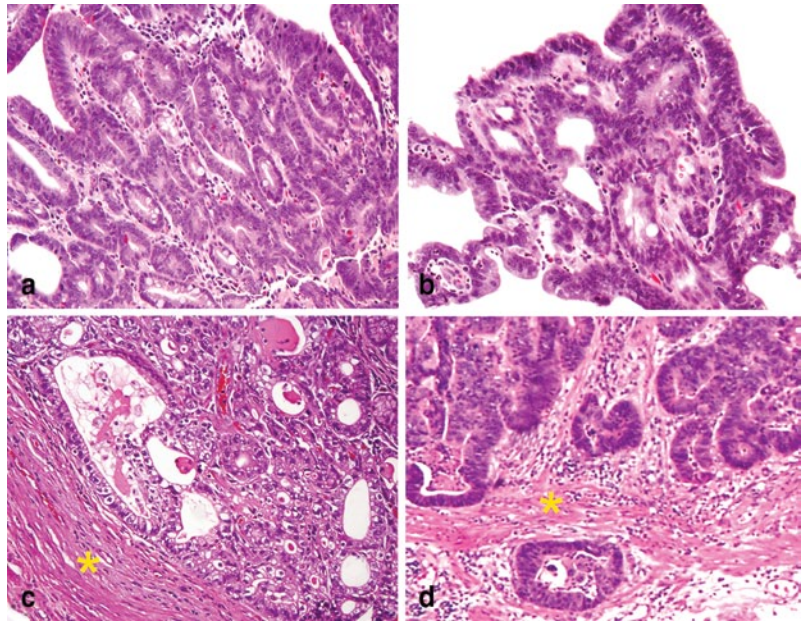

Fig. 4.10 Biopsy diagnosis of early gastric cancer. **a** High-grade glandular dysplasia with crowded glands in the superficial lamina propria is staged as in situ carcinoma (pTis). **b** An example of early gastric adenocarcinoma which exhibits expansile and complex glandular architecture, thus the lesion has progressed beyond high-grade dysplasia. Although stromal invasion cannot be assessed in this superficial biopsy, the tumor should be staged as pT1a. **c** Adenocarcinoma with extensive lamina propria invasion, but the tumor is confined to the mucosa without muscularis mucosae (marked by *) invasion and is staged as pT1a. **d** Adenocarcinoma has invaded thought the muscularis mucosae (marked by *) and into the superficial submucosa, and the tumor is staged as pT1b

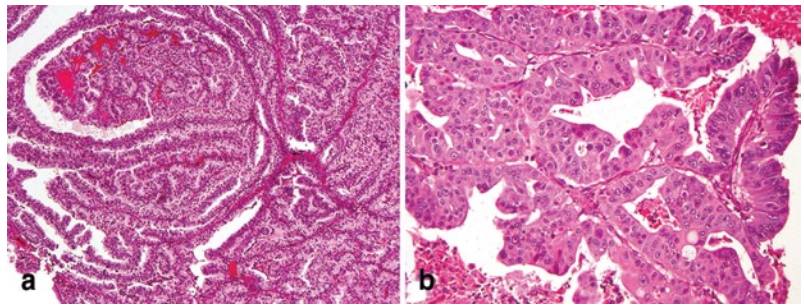

Fig. 4.11 Biopsy diagnosis of detached gastric carcinoma. **a** Papillary variant of gastric adenocarcinoma exhibits well differentiated morphologic and cytologic features with minimal intratumoral stroma. **b** A biopsy of papillary carcinoma may be indistinguishable from high-grade glandular dysplasia

tumor and its relationship to the resection margins. The decision as to where to take the frozen section is at the discretion of the pathologist based upon his/her judgment upon examination of the gross specimen. In the presence of a discrete lesion and gross margin clearance of more than 2 cm, a representative section at the site of the closest margin is adequate. When the tumor diffusely involves the entire stomach, particular in cases of diffuse signet ring cell subtype, it is necessary to submit the entire proximal and margin if this is surgically indicated. When the carci-

noma is present in the mucosal surface, the interpretation of a positive margin is straightforward. Oversight usually occurs when the cancer is present deep in the gastric wall as scattered malignant cells, particularly in cases of diffuse signet ring cell subtype. Therefore, explicit knowledge of the specific subtype of gastric carcinoma facilitates the evaluation of margin status at the time of intraoperative assessment (Fig. 4.12).

Pathologic Stage of Gastric Cancer

The American Joint Committee on Cancer Staging (AJCC) periodically updates their guidelines for staging cancer spread according to the size of the tumor (T-stage), amount of nodal metastasis (N-stage) and the presence or absence of extra-organ metastasis (M-stage). The most recent update occurred in 2010 (Table 4.3) [85].

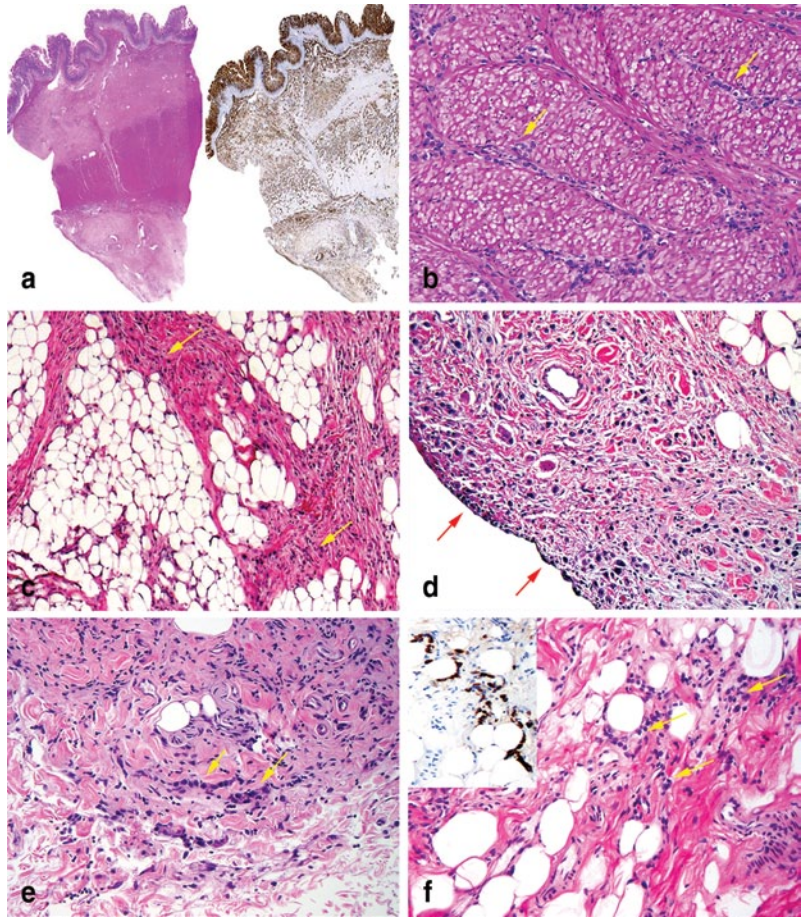

Fig. 4.12 Intraoperative diagnosis of margin status. **a** Diffuse type gastric adenocarcinoma causes thickened gastric wall (*left*) without histologic abnormalities at the mucosal surface. An immunostain of cytokeratin demonstrates transmural infiltration of tumor cells in the gastric wall (*right*). **b** The tumor cells infiltrate between muscular fibers (*arrows*). **c** The tumor cells infiltrates within fibrous septae in subserosal fat (*arrows*). **d** The tumor cells are commonly present at the serosal surface (*arrows*). **e, f** At intraoperative evaluation of the margin status, the tumor may be present in the deep gastric wall as scatted cluster or individual cells, which are better appreciated on an immunostain for cytokeratin

Table 4.3 Gastric cancer TNM staging [85]

Primary tumor (T)		Stage grouping			
TX	Primary tumor cannot be assessed	Stage 0	Tis	N0	M0
T0	No evidence of primary tumor	Stage IA	T1	N1	M0
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria (i.e., high grade dysplasia)	Stage IB	T2	N0	M0
T1	Tumor invades lamina propria (T1a), muscularis mucosae (T1a), or submucosa (T1b)		T1	N1	M0
T2	Tumor invades muscularis propria	Stage IIA	T3	N0	M0
T3	Tumor penetrates submucosal serosa without invasion of visceral peritoneum or adjacent structures		T2	N1	M0
T4	Tumor invades serosa (visceral peritoneum) (T4a) or adjacent structures (T4b)		T1	N2	M0
Regional Lymph Nodes (N)		Stage IIB	T4a	N0	M0
NX	Regional lymph node(s) cannot be assessed		T3	N1	M0
N0	No regional lymph node metastasis		T2	N2	M0
N1	Metastasis in 1 to 2 regional lymph nodes		T1	N3	M0
N2	Metastasis in 3 to 6 regional lymph nodes	Stage IIIA	T4a	N1	M0
N3	Metastasis in 7 or more regional lymph nodes		T3	N2	M0
Distal Metastasis (M)			T2	N3	M0
M0	No distant metastasis	Stage IIIB	T4b	N0	M0
M1	Distant metastasis		T4b	N1	M0
			T4a	N2	M0
			T3	N3	M0
		Stage IIIC	T4b	N2	M0
			T4b	N3	M0
			T4a	N3	M0
		Stage IV	Any T	Any N	M1

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Pathologic Assessment After Neoadjuvant Therapy

Although grading systems for tumor response have not been established, response of tumor to previous chemotherapy or radiation therapy should be reported. The assessment of pathological response to neoadjuvant therapy involves both the gross and the microscopic examination of the resected surgical specimen. At the microscopic level, a positive treatment-related effect is observed as abolition of the malignant epithelium and replacement by dense fibrosis or fibroinflammation. The pathologic response to treatment is determined by the amount of residual viable carcinoma in relation to areas of fibrosis or fibroinflammation within the gross lesion (Fig. 4.13). This relationship can be expressed as the inverse percentage of a favorable treatment response. Thus, a 100 % treatment response indicates fibrosis or fibroinflammation within an entire gross lesion without microscopic evidence of carcinoma,

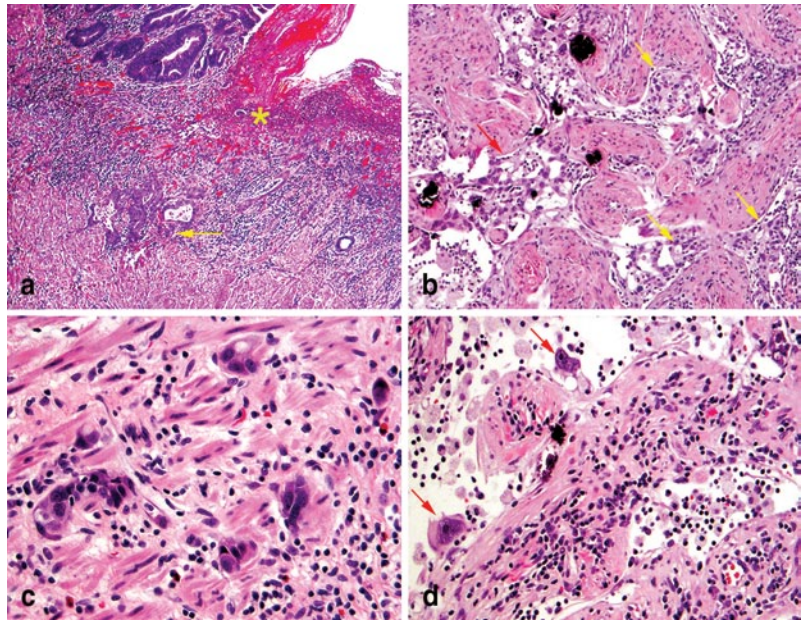

Fig. 4.13 Pathology assessment of gastric carcinoma post neoadjuvant therapy. **a** Gastric mucosa with surface ulceration and fibrin deposition (Marked by *) with clusters of residual carcinoma (*arrow*). **b** Although the carcinoma is mostly viable (*arrow*), the treatment associated changes are apparent which include inflammation, fibrosis, and dystrophic calcification (*dark spots*). **c** Moderate treatment effect with residual carcinoma preset as incomplete glands, small clusters, and individual cells. **d** Marked treatment response with near complete tumor regressions; the residual tumor cells are present as rare single cells (*arrows*)

while a 0 % response represents an entirely viable tumor in the absence of any fibrosis or fibroinflammation. The presence of viable tumor cells suggests incomplete response. Acellular mucin is regarded as a form of positive treatment response, not as viable tumor. The pathologic stage of the residual carcinoma is based on the deepest focus of viable malignant epithelium of the gastric wall. Positive lymph nodes are defined as having at least one focus of viable tumor cells in lymph nodes [86]. As an alternative, 3 category systems also provide good interobserver reproducibility (Table 4.4) [87].

Molecular Pathology of Gastric Carcinoma

Gastric adenocarcinoma develops as a result of an interaction between predisposing environmental conditions, genetic and epigenetic abnormalities, and mutations that affect oncogenes, tumor suppressor genes, and DNA mismatch repair genes [88–90]. The majority of gastric cancers are associated with an infectious etiology, including the *Helicobacter pylori* [91] and Epstein–Barr virus (EBV) [27]. The distribution of histological subtypes of the disease and the frequencies of *H. pylori* and EBV associated gastric cancer vary

Table 4.4 Grading system for tumor regression following administration of neoadjuvant therapy [87]

Description	Tumor regression grade
No viable cancer cells	0 (Complete response)
Single cells or small groups of cancer cells	1 (Moderate response)
Residual cancer outgrown by fibrosis	2 (Minimal response)
Minimal or no tumor kill; extensive residual cancer	3 (Poor response)

across the world [92]. A minority of gastric cancer cases are associated with germline mutation in E-cadherin (CDH1) [93] or DNA mismatch repair genes (Lynch syndrome) [94], whereas sporadic mismatch repair-deficient associated gastric cancers have epigenetic silencing of MLH1 in the context of a CpG island methylator phenotype (CIMP) [95].

Lauren's phenotypic classification of gastric cancer into intestinal or diffuse subtypes has been valuable in providing the basis for providing a genotypic classification of gastric carcinoma. Previously, molecular profiling of gastric cancer has been performed using gene expression or DNA sequencing [72, 96–98]. However, these studies have not led to a pathobiology classification scheme of the disease.

Recently, The Cancer Genome Atlas (TCGA) has developed a robust molecular classification of gastric cancer and identified dysregulated pathways and some candidate driver mutations of distinct classes of gastric cancer [29]. The TCGA studies have characterized four major genomic subtypes of gastric cancer: (1) EBV-infected cancer, (2) MSI cancer, (3) genomically stable cancer, and (4) chromosomally unstable cancer. These molecular subtypes reveal prominent genomic features, and provide a guide to targetable agents. This work will facilitate the development of clinical trials to explore therapies in defined sets of patients, ultimately improving survival from this deadly disease [29].

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Role of HER2 in Gastric Cancers

5

Elizabeth Won and Yelena Y. Janjigian

Introduction

Gastric cancer is diagnosed in over 1 million individuals each year worldwide and the second most common cause of cancer-related death [1]. For localized disease, surgical resection is the cornerstone of curative treatment. Unfortunately, even after curative surgery and peri-operative chemotherapy, many patients will recur and develop metastatic disease. Standard chemotherapy for advanced gastric cancer results in response rates in 20–40 % and median survival of only 8–10 months [2]. There is clearly a need for more specific targeted therapies to improve the current status of systemic treatment beyond conventional chemotherapy. Human epidermal growth factor receptor 2 (HER2) is the first validated treatment target in esophagogastric cancer based on the results of trastuzumab in combination with chemotherapy for treatment of HER2-positive advanced gastric or gastroesophageal junction (GEJ) cancer in the trastuzumab for gastric cancer (ToGA) trial [3].

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HER2 in Esophagogastric Adenocarcinoma

The HER2 oncogene encodes a transmembrane tyrosine kinase receptor that belongs to the epidermal growth factor receptor (EGFR) family. This family is composed of EGFR/HER1, HER2/neu, HER3, and HER4, which play essential roles in promoting cell growth, migration, differentiation, proliferation, and survival. Each receptor has an extracellular domain, lipophilic transmembrane domain, and intracellular tyrosine kinase domain. Activation of the kinase occurs with ligand binding leading to receptor dimerization. HER2 is ligand independent and may be activated due to mutations in HER2 or receptor overexpression [4].

The rates of HER2 amplification or overexpression in esophagogastric cancers vary with the primary location of the cancer. The rates are highest in GEJ or stomach cardia tumors, with 20–30 % HER2 positivity [3]. In the mid and distal stomach 15–20 % are HER2-positive, and only 5–6 % of diffuse or signet ring cell type tumors are positive for the mutation [5, 6].

Diagnosis: HER2 Testing

HER2 testing is recommended in all patients with gastric cancers at the time of diagnosis. HER2 testing for gastric cancers is distinct from breast cancer immunohistochemistry (IHC) testing. Compared to breast cancer, esophagogastric can-

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cers display unique immunostaining characteristics including a high incidence of tumor heterogeneity [7]. In addition, because of the secretory nature of the gastric epithelium, intestinal type gland-forming carcinomas may show incomplete (basolateral or lateral only staining); and these are all considered as a positive result with IHC in addition to complete membrane staining. These differences have been taken into account when developing and validating the HER2 testing protocols specific for gastric cancers [8].

Hoffman et al. proposed the gastric cancer IHC scoring for gastric cancers, which was validated and subsequently used in the ToGA trial.

The current testing guidelines for esophagogastric cancers recommend that IHC should be the initial HER2 testing using validated assays [9, 10]. Samples with equivocal IHC scores of 2+ should be retested by fluorescence in situ hybridization (FISH) or other in situ methods. Cases with 3+ overexpression by IHC or FISH positive (ratio of HER2:CEP17 > 2.0) are considered positive. IHC 0–1+ are considered HER2 negative.

HER2 as a Prognostic Factor

Unlike in breast cancer patients, the role of HER2 positivity as a prognostic factor in gastric cancer remains controversial. A number of retrospective studies have demonstrated that HER2 positivity (by IHC and/or FISH) is a prognostic factor associated with increased risk of invasion, metastasis, and worse survival. In surgical series, HER2 status has been associated as the second poorest prognostic variable after nodal status [11, 12].

However, other studies found no association between HER2 and prognosis in both resectable and advanced stage disease. One large surgical series reviewing 829 resected stage II and III gastric cancer showed that HER2 status was not associated with the overall or recurrence free survival in both univariate and multivariate analyses [13]. Similar findings have been shown in the metastatic setting [14, 15]. The impact of HER2 status was correlated with patient outcome in one large study of 338 advanced gastric cancer patients from six prospective first-line therapeutic trials of chemotherapy without trastuzumab performed in the USA and Europe. Interestingly, the median overall survival was longer in HER2-positive patients (13.9 versus 11.4 months, $p = 0.047$) in the univariate analysis. However, this prognostic value disappeared in multivariate analysis ($p = 0.3$). In addition, the HER2-positive disease was not prognostic in subgroup analysis based on tumor histology [16].

In the ToGA study, the median survival of HER2-positive patients on the control arm (non-trastuzumab) was similar to the historic comparison with phase III studies of 5-Fluoruracil and cisplatin in metastatic gastric cancer [17, 18]. In a recent phase III trial, adding cetuximab to capecitabine and a cisplatin-based chemotherapy, the subset of patients testing HER2-positive had superior outcomes compared to HER2 negative patients, irrespective of the therapy [19]. Unlike breast cancer where HER2-positive disease carries an adverse prognostic value, the prognostic role of HER2 overexpression in advanced or resectable gastric cancers remains unclear at this time.

Trastuzumab for HER2-Positive Gastric Adenocarcinoma

ToGA Study

Trastuzumab (Herceptin®, Genentech) is a monoclonal antibody which binds to the extracellular domain of the HER2. It mediates antibody-dependent cellular cytotoxicity by inhibiting proliferation of cells that overexpress HER2 protein, resulting in the blockade of receptor dimerization. Trastuzumab is a key component in the treatment of early and metastatic HER2-positive breast cancer [20–22].

The ToGA trial is the first prospective, multicenter, phase III trial to evaluate the efficacy and safety of trastuzumab in patients with HER2-positive gastric and GEJ adenocarcinoma in combination with standard chemotherapy. In this trial,

594 patients with HER2-positive (3+ on IHC or FISH positive HER2:CEP17 ratio ≥2) were randomized to receive cisplatin and fluoropyrimidine alone or with trastuzumab. Patients assigned to receive trastuzumab with chemotherapy had a significant improvement in all measures of efficacy including OS (13.8 versus 11.1 months, HR 0.74, 95%CI 0.60–0.91, $p=0.0046$), progression-free survival (PFS, 6.7 versus 5.5 months, HR 0.71, 95%CI 0.59–0.85, $p=0.0002$), and overall response rate (47 versus 35%, $p=0.0017$) [3].

Trastuzumab is the first biological agent to show a survival benefit in the treatment of advanced esophagogastric adenocarcinoma. In October 2010, the Food and Drug Administration (FDA) granted approval for trastuzumab in combination with cisplatin and a fluoropyrimidine (either capecitabine or 5-fluorouracil) for the treatment of patients with HER2-positive metastatic gastric or GEJ adenocarcinoma who have not received prior treatment for metastatic disease based on the results of the ToGA trial.

Trastuzumab is administered at an initial dose of 8 mg/kg intravenously (IV) followed by 6 mg/kg IV every 3 weeks until disease progression or intolerable toxicity. The most common grade 3 or 4 toxicities in patients treated with trastuzumab plus chemotherapy were neutropenia, anemia, diarrhea, nausea, anorexia, and vomiting. Of all patients receiving trastuzumab plus chemotherapy, 37% developed infusion-related reactions. Cardiac adverse reactions were rare, with no difference between the two groups. Cardiac failure occurred in less than 1% of patients.

Predictors of Response to Trastuzumab

Currently there are no predictive biomarkers of response to trastuzumab. In breast cancer, the level of HER2 amplification has only been shown to be truly predictive in the neoadjuvant setting [23].

In the post hoc subgroup analysis of the ToGA trial, patients with strongly HER2-positive tumors (IHC 2+/FISH+ or IHC 3+) derived the greatest OS benefit with the addition of trastuzumab to chemotherapy (16.0 versus 11.8 months, HR 0.68, 95% CI 0.5–0.83). In an exploratory study, Gomez-Martin et al. evaluated 90 patients with metastatic gastric cancer treated with first-line trastuzumab-based chemotherapy to evaluate the relationship between HER2/CEP17 ratio and HER2 gene copy numbers with outcome [24]. Central testing for HER2 status using IHC and dual color silver in situ hybridization (de-SISH) was performed on all tumors. In the study, the authors found that a mean HER2/CEP17 ratio of 4.7 was identified as the optimal cutoff value discriminating trastuzumab sensitive and refractory patients ($p=0.005$). The optimal cutoff for predicting survival longer than 12 months was 4.45 ($p=0.005$) and for survival longer than 16 months was 5.15 ($p=0.004$). For HER2 gene copy numbers, the optimal cutoff values were 9.4, 10.0, and 9.5, respectively for the outcomes ($p=0.02$). The relationship between the level of HER2 amplification and outcome of HER2 gastric cancer treated with trastuzumab requires further investigation.

Dose Escalation of Trastuzumab

It has been suggested that the pharmacokinetics of trastuzumab differ in gastric cancer and breast cancer patients, and higher dosing may be required in gastric cancer patients. Pharmacokinetic data reported from the ToGA study showed that the trastuzumab clearance is 0.378 L day based on the current standard dosing, 70% higher than the clearance rates shown in patients with metastatic breast cancer receiving trastuzumab [25, 26].

In addition, research in breast cancer has shown that patients with greater sites of metastatic disease have faster clearance of trastuzumab [25]. The greater tumor burden seen in metastatic gastric cancer patients may be associated with higher clearance levels of trastuzumab, and thus gastric cancers patients may require higher dosing.

The HELOISE study is an ongoing study designed to compare standard versus escalated dose

of trastuzumab in HER2-positive metastatic gastric and GEJ cancers in combination with cisplatin-based chemotherapy [27]. In this phase III multicenter study, patients are randomized to either standard dosing or higher dosing arm (trastuzumab given at 8 mg/kg loading dose followed by 10 mg/kg every 3 weeks). The accrual goal is for 400 patients, with primary endpoint of overall survival and secondary endpoints evaluating safety, trastuzumab concentrations, PFS, and response rates. At present time, only the standard dosing of trastuzumab is approved for advanced or metastatic gastric and GEJ cancers.

Trastuzumab in the Adjuvant or Neoadjuvant Setting

Unlike in breast cancer, currently trastuzumab is only indicated in the setting of HER2-positive advanced or metastatic disease in gastric cancer. Given the success of HER2 directed therapies in both neoadjuvant and adjuvant breast cancer, the use of trastuzumab in the adjuvant and neoadjuvant setting is an area of active investigation in gastric cancer research.

There is a small ongoing phase II study planning to accrue 45 patients with resectable HER2-positive gastric or GEJ adenocarcinoma to receive three cycles of neoadjuvant chemotherapy with oxaliplatin, capecitabine, and trastuzumab. Patients achieving R0 or R1 resection will receive a further three cycles of the same chemotherapy regimen postoperatively with trastuzumab continuing for 12 months [28]. RTOG 1010 trial is a phase III trial evaluating radiation, paclitaxel, and carboplatin with or without trastuzumab in locally advanced HER2 overexpressing esophageal and GEJ adenocarcinoma with a planned enrollment of 160 patients with the anticipation of screening 480 patients [29].

In the adjuvant setting, there is an active phase II study of oxaliplatin, capecitabine, trastuzumab, and chemoradiotherapy in patients with curatively resected HER2-positive gastric or GEJ adenocarcinoma (TOXAG study) [30]. It is hoped that these studies will provide data regarding the efficacy of trastuzumab for resectable gastric cancer.

Mechanisms of Trastuzumab Resistance

Resistance to trastuzumab is now emerging in HER2-positive esophagogastric cancers after median of 6.7 months [3]. There is no standard of care second-line therapies for HER2-positive gastric cancer after progression on trastuzumab. Mechanisms of resistance are being actively investigated.

Several putative models of resistance have been described in HER2-positive breast cancer [31]. Activation of PI3K-AKT-mTOR signaling pathway by loss of phosphatase and tensin homolog (PTEN) suppressor and mutation activation of PI3K has been demonstrated to confer resistance to trastuzumab in preclinical studies [32]. Increased signaling from HER family receptors (including overexpression of HER3 and formations of high levels of HER2-HER3 heterodimers) and insulin-like growth-like growth factor-1 receptor (IGF-1R) are also associated with PI3K-AKT activation and trastuzumab resistance [33]. Another proposed mechanism is the accumulation of a truncated form of the HER2 receptor, p95, which lacks the extracellular domain needed for trastuzumab binding [30].

EGFR plays a significant role in trastuzumab resistance. Work by Ritter and colleagues demonstrated that trastuzumab resistant cell lines and xenograft models overexpress phosphorylated EGFR, EGFR/HER2 heterodimers, and HER family ligand EGFR, heparin-binding EGF, and heregulin [34]. Furthermore, the addition of dual EGFR/HER2 kinase inhibitors was shown to lead to diminished HER2 phosphorylation and cellular proliferation [34].

The role of EGFR/HER2 cross-talk in transformation and tumor progression is supported by multiple examples in mouse models and primary human tumors. For example, co-expression of the EGFR ligand TGFα and Neu in the mammary gland of transgenic mice markedly accelerates tumor onset and progression compared with mice expressing the TGFα or Neu transgenes alone. In this model, bitransgenic mice exhibited increased tyrosine phosphorylation of both EGFR and HER2 and tumor latency was markedly de-

layed by the administration of the EGFR tyrosine kinase inhibitor (TKI). [35, 36]. Analysis of breast tumor specimens revealed that the majority of breast tumors with phosphorylated HER2 at Y1248 exhibited detectable EGFR and the combination of Y1248 phosphorylated HER2 together with the co-overexpression of HER2 and EGFR is associated with the shortest patient survival [37]. In esophagogastric cancers, EGFR is commonly overexpressed and may signify worse prognosis [38, 39]. Although EGFR overexpressing MKN7 gastric cancer cells are insensitive to trastuzumab, in these cells, submicromolar concentrations of an EGFR TKI, gefitinib, inhibit p-EGFR and restore sensitivity to trastuzumab [34]. Combined blockade for EGFR and HER2 may be a viable strategy to overcome trastuzumab resistance.

Novel and Combination Therapies

A number of strategies for overcoming trastuzumab resistance have been proposed and new agents are being actively studied in gastric cancers. These include clinical trials testing agents in gastric cancer already approved for HER2-positive breast cancers.

Pertuzumab

Pertuzumab (Perjeta®, Genentech) is a human monoclonal antibody which binds to extracellular domain HER2. Unlike trastuzumab which binds at domain IV of the HER2 receptor, pertuzumab binds at domain II of the receptor and is thus able to disrupt HER2 heterodimerization and ligand-activated signaling with other HER family members, including EGFR, HER3, and HER4. The HER2-HER3 heterodimer is an effective activator of the PI3K signaling pathway; blockade of HER2-HER3 complexes likely represents the most relevant antitumor action of pertuzumab. In HER2+ breast cancer, pertuzumab in combination with trastuzumab and docetaxel demonstrated significant improvement in PFS compared to placebo, trastuzumab, and chemotherapy in advanced disease [40]. In the neoadjuvant treatment of HER2+ breast cancer, the combination of pertuzumab, trastuzumab, and chemotherapy showed significantly increased pathological complete responses compared to other regimens, leading to FDA approval in both the advanced and neoadjuvant settings [41].

Yamashita-Kashima and colleagues investigated the antitumor activity of pertuzumab in combination with trastuzumab in HER2+ gastric cancer xenograft models. Their results demonstrated antitumor activity with pertuzumab monotherapy and more potent activity with the combination of pertuzumab and trastuzumab. In addition, the combination of the two agents reduced EGFR-HER3 heterodimerization and phosphorylation of these receptors and their downstream signaling factors [42].

The clinical efficacy of pertuzumab in breast cancer and the in vivo activity in HER2-positive gastric cancers lead to development of the international phase III JACOB study in HER2-positive metastatic gastric or GEJ patients. This ongoing multicenter international study randomizes patients to receive pertuzumab or placebo in combination with trastuzumab, cisplatin, and fluoropyrimidine as first-line therapy [43]. Target enrollment is 780 patients. The results of this study are eagerly awaited.

TDM-1

Antibody-drug conjugates are a way to deliver cytotoxic drugs directly to cancer cells. TDM-1 (Kadcyla, Genentech) is an antibody-drug conjugate of trastuzumab and emtansine, a microtubule inhibitor. In metastatic HER2-positive breast cancer patients previously treated with trastuzumab and a taxane, TDM-1 was shown to improve PFS by 3.2 months and OS by 5.8 months compared to patients treated with lapatinib plus capecitabine [44]. This led to the FDA approval of the first antibody drug conjugate to show activity in breast cancer.

In preclinical gastric cancer models, TDM-1 has shown more effective tumor activity than trastuzumab [45]. In combination with pertu-

zumab, TDM-1 has been shown to increase binding of TDM1-1 to HER potentially augmenting antibody-dependent cellular cytotoxicity and result in downstream HER2 signaling [46].

A multicenter adaptive phase II/III of TDM-1 is currently recruiting patients with HER2-positive advanced gastric cancer after progression on first line treatment. Patients will be randomized to one of three treatment arms: TDM-1 at 3.6 mg/kg every 3 weeks, TDM-1 at 2.4 mg/kg every week, or standard taxane chemotherapy (docetaxel or paclitaxel, per physician choice). After 100 patients in all three study arms have been treated for at least four cycles, the dose and schedule of trastuzumab will be determined and used in the second stage of the study, with overall survival as the primary endpoint [47].

Reversible EGFR/HER2 TKIs: Lapatinib

Lapatinib (Tykerb®, GlaxoSmithKline) is a reversible TKI of EGFR and HER2 that blocks activation by binding to the intracellular adenosine triphosphate (ATP) binding site of these kinases. Lapatinib has shown activity in HER2-positive breast cancer phase II and III clinical trials and causes response in some patients refractory to trastuzumab, suggestion that suppression of HER2 continues to be useful in this population [48, 49]. Modest activity was demonstrated with single-agent lapatinib in esophagogastric adenocarcinomas. In the Southwest Oncology Group (SWOG) 0413 trial, unselected patients showed a 9% confirmed partial response rate, and 23% had disease stabilization [50]. HER2 overexpression was not required for participation in this study which affected the potential efficacy of the drug.

However, two large phase III trials of lapatinib indicated no signal of activity for lapatinib in confirmed HER2-positive gastric cancer patients. The LOGiC trial is a phase III trial of capecitabine and oxaliplatin with or without lapatinib in first-line advanced HER2 FISH amplified gastric and GEJ adenocarcinoma. The presented results show that the lapatinib arm did not meet its primary endpoint of overall survival (HR 0.91, 95% CI 0.73, 1.12, $p=0.35$ in the lapatinib arm), but there were improvements in survival only in subgroups (Asian patients, HR 0.68; patients under 60 years of age, HR 0.69) [51] .

TyTAN is a completed open-label randomized phase III study comparing paclitaxel with paclitaxel plus lapatinib in patients with HER2 FISH-amplified gastric cancer as a second-line therapy [52]. In 261 East Asian patients, the median OS for the lapatinib plus paclitaxel group was 11.0 months compared to 8.9 months alone in the paclitaxel group, which was not statistically significant (HR 0.84, $p=0.2$). In a preplanned subgroup analysis, in HER2 IHC3+ patients the median OS was 14.0 months in the lapatinib combination group compared to 7.6 months for paclitaxel alone (HR 0.59, $p=0.0176$). In this study, patients were required to have HER2 amplified gastric cancer in order to be eligible; however this did not correlate with HER2 positivity by IHNC. 35% of patients had tumors classified as IHC0/1+, which may account for the survival benefit seen only in the subgroup of IHC 3+ patients.

Irreversible EGFR/HER2 TKIs: Neratinib, Afatinib

In vitro data suggest that second-generation irreversible inhibitors covalently bind HER2 and EGFR (unlike lapatinib, which compete with intracellular ATP in a reversible manner) in a highly selective fashion, which may be able to overcome trastuzumab resistance. In HER2-positive breast cancer patients with trastuzumab resistance, the reported efficacy profile seen with one such irreversible, dual EGFR/HER2 inhibitor (neratinib) compares favorably with the monotherapy experiences with anti-HER2 agents. Treatment with neratinib resulted in 16-week PFS rates of 59% and objective response rates of 24% in patients with prior trastuzumab treatment [53]. In the phase II I-SPY 2 trial, neratinib produced a significantly improved pathological complete response at the time of surgery in patients with stage II/III HER2-positive, hormone receptor negative breast tumors, compared with a control group (55 versus 32%) [54]. With these promising results, a phase III trial is currently underway, comparing

neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive patients who have received two or more prior anti-HER2 regimens [55]. There is an ongoing multicenter open-label phase 2 study of neratinib in patients with solid tumors with HER2, HER3, or EGFR mutations, which is open to patients with HER2-positive gastric cancer [56]. Study accrual is ongoing.

Afatinib (Gilotrif®, Boehringer Ingelheim) is another irreversible inhibitor of EGFR, HER2, and HER4. In July 2013, the FDA approved afatinib for the first-line treatment of patients with metastatic non-small cell lung cancer whose tumors had specific EGFR gene mutations (exon 19 deletions or exon 21 (L858R) substitution mutations) as detected by an FDA approved test. Afatinib is currently in phase III development in EGFR positive non-small cell lung cancer, trastuzumab pretreated HER2 breast cancer, and head and neck squamous cell carcinoma.

There is preclinical data showing potent antitumor activity of single agent afatinib in an NCI-N87 HER2-positive esophagogastric cancer xenograft. Although the tumors were relatively refractory to trastuzumab, treatment with single agent afatinib led to dramatic tumor volume regression. The combination of afatinib with trastuzumab had even greater antitumor efficacy than either drug alone [57]. These results are similar to the clinical experiences seen in breast cancer patients. Blackwell et al. showed that despite disease progression on prior trastuzumab-based therapy, lapatinib in combination with trastuzumab significantly improves PFS and clinical benefit rate versus lapatinib alone, thus offering a chemotherapy-free option with an acceptable safety profile to patients with HER2-positive metastatic breast cancer [49].

Simultaneous targeting of EGFR/HER2 kinase activity may be an effective strategy in patients with metastatic, trastuzumab resistant HER2-positive esophagogastric cancer via potent signaling inhibition. There is an ongoing phase II study of afatinib in combination with trastuzumab in metastatic HER2-positive trastuzumab refractory esophagogastric cancer [58]. The first cohort of patients in the study was treated with afatinib alone. Preliminary results reported in these 14 patients showed promising activity, with one patient with confirmed partial response (PR), and three patients with disease stabilization [59]. The second cohort of the study will receive the combination of afatinib and trastuzumab.

Future Directions

Functional Imaging

The clinical efficacy of anti-HER therapies is dependent on the level of HER2 expression in both breast and gastric cancers. Currently, the two approved techniques to evaluate HER2 expression include IHC and FISH. However, as discussed previously in this chapter, the HER2 expression of esophagogastric cancers can be heterogenous and show incomplete staining on IHC. Furthermore, in breast cancers, it has been shown that HER2 expression can be discordant between the primary lesion and distant metastatic disease, and may also vary between metastatic lesions [60–63].

The development of radiolabeled antibodies is an active area of research. Position emission tomography (PET) imaging of HER2 with radiolabeled trastuzumab may allow PET imaging to quantitate HER2 expression levels and guide therapy selection and allow for monitoring of response. Such a technology would allow for noninvasive assessment of HER2 expression in the primary tumor and all sites of metastases simultaneously, a clear potential advantage over single site biopsies. Furthermore, the biodistribution of trastuzumab can vary in each patient and is heavily impacted by the extent of tumor load, which may contribute to variations in patient responses [64, 65]. Use of functional imaging technology may thus help elucidate the molecular basis of resistance to trastuzumab. Studies have evaluated trastuzumab radiolabeled with Indium-111 (^{111}In), Copper-64 (^{64}Cu) in xenograft cancer models.

Zirconium-89 (^{89}Zr) is an attractive radionuclide for use in functional PET imaging due to its favorable characteristics, with a half-life of 78 h, and shown to be stable with respect to ligand

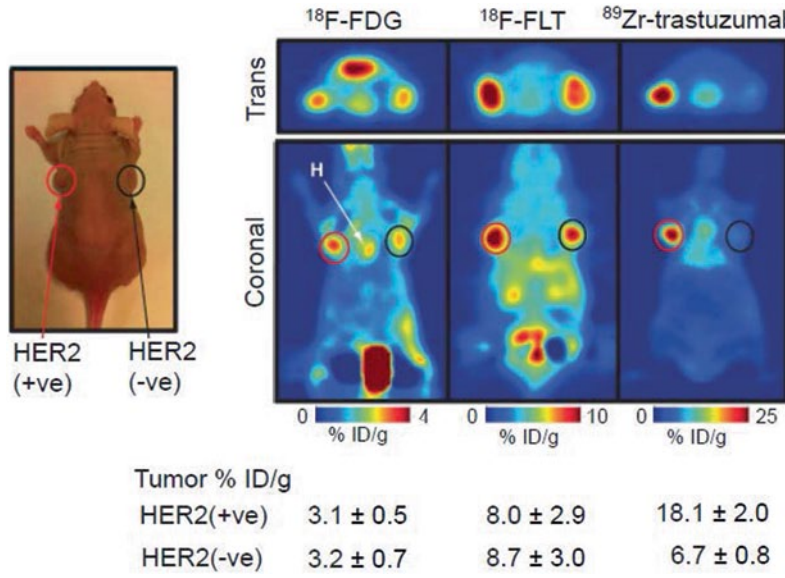

Fig. 5.1 Specificity of ^{89}Zr-trastuzumab for HER2-positive tumors. Coronal ^{89}Zr-trastuzumab, ^{18}F-FDG, and ^{18}F-FLT PET images of athymic nude mice bearing subcutaneous HER2-positive NCI-N87 (*left*) and HER2-negative MKN-74 (*right*) tumors are shown. *+ve* = positive; *−ve* = negative. This research was originally published in JNM. (Janjigian YY, Viola-Villegas N, Holland JP, et al. [57]; images on the right: © by the Society of Nuclear Medicine and Molecular Imaging, Inc.)

disassociation in human serum for greater than 7 days. The first in-human ^{89}Zr-trastuzumab PET imaging study showed excellent tumor uptake and visualization of HER2-positive breast metastases, including in-brain tumor lesions [66]. Xenograft studies performed by researchers at Memorial Sloan Kettering Cancer Center (MSKCC) have demonstrated that ^{89}Zr-trastuzumab PET is highly specific for HER2-positive gastric tumors, whereas as 18-FDG and 18-FLT PET were unable to differentiate HER2-positive from HER2 negative tumors (Fig. 5.1) ^{89}Zr-trastuzumab PET is now being evaluated by this group in humans with HER2-positive esophagogastric cancers [67].

Patient-Derived Xenografts

Individual esophagogastric cancer subtypes have heterogenous tumor characteristics and clinic outcomes, making this malignancy a complex disease to treat. Cell culture lines and even mouse xenografts of human tumor cell lines have had variable predictive power in the translation of cancer therapies into clinical setting [68]. These models often fail to reproduce the complexities of the tumor microenvironment and the interaction between the tumor cells and the immune system, which are integral components to tumor proliferation and metastasis [69].

Tumor graft models or patient-derived xenografts (PDXs) are being studied as an alternative, more clinically predictive model of human malignancies. PDXs are based on the transfer of primary tumors directly from the patient into an immunodeficient mouse. The tumors can be implanted either heterotopically or orthotopically. Heterotopic PDX model involves implanting tumors into the subcutaneous tissue of the mouse. Orthotopic models involve direct implantation of the tumor into a specific mouse organ. The heterotopic method allows for easier cell transfer and precise monitoring of tumor growth. The orthotopic models, while more technically challenging, are considered to more accurately mimic the human tumors [70]. Limitations of using PDX models for research include the higher cost

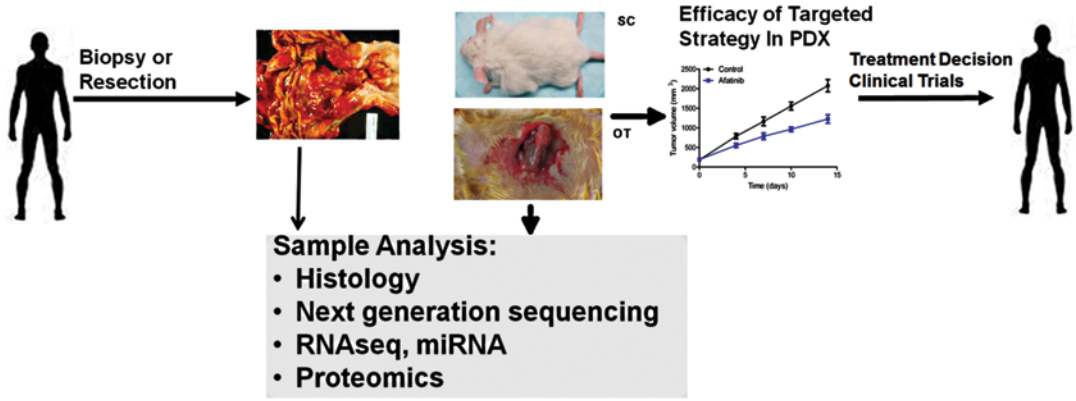

Fig. 5.2 MSKCC Patient-Derived Xenograft (*PDX*) Program Schema: esophagogastric cancer models implemented to bring targeted agents to the clinic

and more specialized maintenance compared to cultured cell lines. Furthermore, PDX models can require long latency periods after engraftment and variable engraftment rates between 23 and 75 % depending on the tumor type [69, 71].

PDX models are actively being studied in esophagogastric cancers. Janjigian and colleagues at MSKCC have established both heterotopic and orthotopic PDX models using nonobese diabetic/severe combined immunodeficient (NOD/SCID) mouse (Fig. 5.2). The established PDXs include HER2-positive trastuzumab refractory models, MET+ models, and signet ring gastric model with germ line CDH1 mutation. Tumor engraftment rates of 46 % for orthotopic tumors and 26 % for heterotopic implants were reported [72]. PDX models are a promising platform to further validate differences in tumor biology and guide the design of clinical trials. Further, molecular profiling and therapeutic experiments with the PDX models are underway to identify distinct molecular signatures predictive of response to these agents.

Genomic Sequencing

Next generation sequencing (NGS) has allowed for cheaper and faster sequencing compared to traditional Sanger sequencing. The Cancer Genome Atlas (TCGA) is an ongoing research program supported by the National Cancer Institute and National Human Genome Research Institute at the National Institutes of Health. The TCGA researchers will identify the genomic changes in more than 20 different types of human cancer, including gastric and esophageal cancers. The genomic sequencing data will be available to the research community and allow for a more comprehensive understanding of the acquired genetic, genomic, and epigenetic alterations in cancer cells that can be translated into clinical and therapeutic advances.

The integrated esophagogastric TCGA data provide insight in the tumorigenesis of gastric cancers and identify further targetable mutations, beyond HER2. Whole exome and genome sequencing of esophageal adenocarcinoma tumors and normal pairs identified 26 significantly mutated genes. The sequencing identified novel mutated genes not previously implicated in this disease, including mutations in chromatin modifying factors and candidate contributors: *SPG20, TLR4, ELMO1, and DOCK2* [73]. The esophagogastric TCGA identified four distinct subsets of the disease: (1) Epstein Barr Virus (EBV) tumors with marked methylation, PIK3CA mutations, PD-L1/2 amplification, (2) Tumors with Microsatellite instability (MSI) and frequent activating mutations, (3) chromosomally instable (CIN) tumors with frequent oncogenic amplifications, and (4) chromosomally stable/diffuse type tumors with novel mutations of *RHOA* (ras homolog gene family, member A). *RHOA* encodes a

small guanosine-5′-triphosphatase (GTPase) that displays potent oncogenic activity when overexpressed. Recent TCGA sequencing data on diffuse-type gastric carcinoma revealed newly identified recurrent *RHOA* hotspot mutations in diffuse-type gastric cancers, which were not seen in intestinal-type tumors [74, 75]. The presence of *RHOA* mutations was associated with tumors located in the cardia, poorer tumor differentiation, and less likely to be associated with TP53 mutations. Further detailed mechanistic and translational studies are ongoing [74].

At Memorial Sloan Kettering Cancer Center, NGS using the integrated mutation profiling of actionable cancer targets (IMPACT) assay is being performed to identify previously unrecognized biomarkers of drug sensitivity and resistance. The IMPACT assay is capable of identifying point mutations, small insertion/deletion events (indels), and large gene level and intragenic copy number aberrations in 275 cancer-associated genes. In the ongoing phase II study of afatinib in metastatic HER2-positive, trastuzumab refractory cancer, pre- and posttreatment biopsies are being collected in all patients, allowing for a unique opportunity to define the prevalence of p95-HER2 and other genetic aberrations that have been associated with trastuzumab resistance in preclinical models [57].

Genomic sequencing technology will allow for the comprehensive profiling of tumor specimens and holds the potential to guide cancer treatment. Efforts are ongoing at institutions worldwide to correlate the genetic and molecular information of the genomic sequencing data with clinical data to guide individualized therapies and diagnostic tools.

Conclusions

The majority of patients with gastric cancer present with advanced disease, which is incurable. Molecularly targeted therapies, such as those targeting HER2, are anticipated to improve the current status of systemic treatment beyond conventional cytotoxic therapy. Trastuzumab in combination with chemotherapy in patients is the first molecular agent in metastatic HER2-positive gastric and gastroesophageal to result in improvements in response rates, time to progression and survival. Trastuzumab is now being investigated in the neoadjuvant and adjuvant setting. Unfortunately, as with breast cancer, many esophagogastric patients will develop resistance to trastuzumab. Several promising therapeutic agents are currently under investigation as monotherapy and in combination with chemotherapy in the first and second line setting. New avenues of research into mechanisms of resistance and technology to better diagnose and treat HER2 gastric cancer are being actively studied.

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Pathophysiology of Hereditary Diffuse Gastric Cancer

6

Sharon Pattison and Alex Boussioutas

Abbreviations

DGC	Diffuse gastric cancer
EMT	Epithelial to mesenchymal transition
EPIC	European Prospective Investigation into Cancer and Nutrition
FAP	Familial adenomatous polyposis
FDG	fluoro-2-deoxy-D-glucose
FDGC	Familial diffuse gastric cancer
GC	Gastric cancer
GI	Gastrointestinal tract
HDGC	Hereditary diffuse gastric cancer
HNPCC	Hereditary non-polyposis colorectal cancer
IGCLC	International Gastric Cancer Linkage Consortium
LBC	Lobular breast cancer
MLPA	multiplex ligation-dependent probe amplification
PET	Positron emission tomography
SRC	Signet ring cell
SRCC	Signet ring cell carcinoma

Introduction

Familial gastric cancer (GC) with an autosomal dominant pattern has been documented for many years, the earliest possibly being Napoleon Bonaparte's family, with a number of his family members potentially succumbing to GC [1–3]. Approximately 1–3 % of all GCs are now thought to occur as part of a known hereditary syndrome [4–8]. The most common hereditary syndrome associated with GC is hereditary diffuse gastric cancer (HDGC) (MIM#137215), an autosomal dominant condition that results in the development of diffuse gastric cancer (DGC), as classified by the Lauren classification [9], (see Chap. 4: Pathologic classifications) and typically diagnosed at a younger age than sporadic GC [10, 11]. The gene responsible for HDGC was identified as the cadherin 1 (*CDH1*) gene or E-cadherin (see section below). The penetrance of disease in carriers is high, but not complete. Carriers of a *CDH1* mutation have a lifetime risk of developing GC of approximately 80 % [7]. Surveillance for DGC of known mutation carriers is problematic because of the difficulty in identifying DGC at an early stage. Carriers are often asymptomatic, and may have no evidence of disease on surveillance investigations, but at gastrectomy are often found to harbour multifocal intramucosal signet ring cells (SRCs), consistent with early carcinoma, throughout the stomach. These SRC lesions are frequently multifocal and are characteristically indolent. Once a family is identified as at-risk of HDGC by clinical criteria, they are referred to appropriate genetic services for genetic diagnosis and multidisciplinary management that usually requires carriers to have prophylactic gastrectomy.

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Genetics

E-Cadherin

HDGC is caused by germline mutations of the E-cadherin gene or (CDH1). CDH1 mutations were first identified in HDGC kindreds by linkage analysis of three New Zealand Maori families with multigeneration, early onset DGC in 1998 [12]. The family in which the *CDH1* gene mutation was identified was originally published in 1965 [13], and remains the largest published HDGC kindred. Family members from this kindred had a median age of death from GC of 33 years, with the youngest documented death occurring at the age of 14 [12, 13]. Since this discovery, mutations in *CDH1* have been identified in HDGC families from diverse ethnic backgrounds [14–24]. The pattern of inheritance is autosomal dominant with incomplete penetrance.

CDH1 (MIM# 192090) encodes epithelial-cadherin (E-cadherin), a transmembrane calcium-dependent cell adhesion glycoprotein that plays an essential role in morphogenesis, the maintenance of normal polarised epithelium, and interacts through catenins with the actin cytoskeleton [25–27]. *CDH1* is located on 16q21.1, and consists of 16 exons with a CpG island upstream of the coding region [28]. The translated E-cadherin protein consists of three major domains, a large extracellular domain (encoded by exons 4–13) and smaller transmembrane (exons 13–14) and cytoplasmic domains (exons 14–16) [25, 26].

Somatic mutations in the *CDH1* gene were described in DGC before the recognition of HDGC [29–33]. Abnormal E-cadherin expression or mutations have also been found in sporadic lobular breast cancer (LBC) [34], prostate cancer [35] and carcinomas of the endometrium and ovary [36].

In HDGC, mutations are seen over the length of the *CDH1* coding sequence, and include point mutations, and small insertions and deletions. More recently, larger deletions have also been identified [37–39]. Table 6.1 describes the published *CDH1* mutations found in HDGC fam-

Table 6.1 Published *CDH1* mutations in HDGC families

Exon	Mutation	Mutation type	Ref.	Exon	Mutation	Mutation type	Ref.
1	Del exon 1–2 (19353 bp)	Truncation	[37]	10	1397-1398delTC	Frameshift	[24, 41]
	Del exon 1–2 (5761 bp)	Truncation	[37]		1466insC	Frameshift	[42]
	Del 5'UTR-exon 1 (150 bp)	Truncation	[37]		1470-1483del	Truncation	[43][b]
	2T>C	Initiation codon	[44]		1472insA	Frameshift	[21]
	3G>C	Initiation codon	[45]		1476delAG	Frameshift	[20]
	41delT	Frameshift	[46]		1488-1494del CGAGGAC	Frameshift	[15]
	45insT	Frameshift	[21]		1507C>T	Nonsense	[47]
	46insTGC	Frameshift	[44]		1565+1G>A	Splice site	[48]
	49-2A>C	Splice site	[41]		1565+1G>T	Splice site	[22]
	49-2A>G	Splice site	[19]		1565+2insT	Splice site	[49]
	49G>T	Splice site	[50]		1565+2dup	Splice site	[43]
2	53delC	Frameshift	[22]	11	1588insC	Frameshift	[15]
	59G>A	Nonsense	[19]		1595G>A	Nonsense	[43][b]
	70G>T	Nonsense	[15]		1610delC	Frameshift	[51]
3	164-?387+?del	Nonsense	[38]		1619insG	Frameshift	[52]
	185G>T	Missense	[53]		1682insA	Frameshift	[24]
	187C>T	Nonsense	[17, 45]		1679C>G	Missense	[43]
	190C>T	Nonsense	[15]		1710delT	Frameshift	[22]

Table 6.1 (continued)

Exon	Mutation	Mutation type	Ref.	Exon	Mutation	Mutation type	Ref.
	283C>T	Nonsense	[23, 24], [43][b]		1711insG	Frameshift	[17]
	353C>G	Missense	[41]		1711+5G>A	Splice site	[20]
	372delC	Frameshift	[16]	12	1774G>A	Missense	[24][a]
	377delC	Frameshift	[24]		1779insC	Frameshift	[20]
	382delC	Frameshift	[20]		1792C>T	Nonsense	[17, 22, 45, 54]
4	469delG	Frameshift	[43]		1795A>T	Missense	[24][a]
	531+2T>A	Splice site	[55]		1849G>A	Missense	[56]
5	586G>T	Nonsense	[15]		1901C>T	Missense	[24, 41, 56, 57]
	687+1G>A	Splice site	[20]		1913G>A	Nonsense	[24]
6	715G>A	Missense	[24, 41, 58]	13	2061delTG	Frameshift	[20]
	731A>G	Missense	[24, 59]		2064delTG	Frameshift	[20, 49]
	753insG	Frameshift	[44]		2095C>T	Nonsense	[12, 41]
7	Del exon 7–16	Truncation	[39]		2161C>G	Splice site	[45]
	832G>A	Splice site	[18, 21]		2164+2T>A	Splice site	[43]
	832+1G>T	Splice site	[43]		2164+5G>A	Splice site	[22, 24]
	833-2A>G	Splice site	[49, 60]	14	Del exon 14–16 (8078 bp)	Truncation	[37]
	892G>A	Missense	[20]		2195G>A	Missense	[20, 24]
	1003C>T	Nonsense	[45, 49, 61, 62]		2245C>T	Missense	[24]
	1008G>T	Splice site	[12]		2269G>A	Missense	[63]
8	1017delC	Frameshift	[41]		2275G>T	Nonsense	[64]
	1018A>G	Missense	[21, 56, 65]		2276delG	Frameshift	[45]
	1023T>G	Nonsense	[44]	15	2295+5 G>A	Splice site	[22]
	1062delG	Frameshift	[24][a]		2287G>T	Nonsense	[66]
	1064insT	Frameshift	[20]		2310delC	Frameshift	[20]
	1107delC	Nonsense	[41]		2329G>A	Missense	[24]
	1118C>T	Missense	[67]		2343A>T	Missense	[24][a], [43][b]
	1134del8ins5	Frameshift	[20]		2381insC	Frameshift	[12]
	1135+5del8ins5	Splice site	[68]		2386delC	Frameshift	[43]
	1137G>A	Splice site	[24, 41, 43, 55]		2395delC	Frameshift	[49]
	1137+1G>A	Splice site	[15]		2396C>G	Missense	[52]
9	1147C>T	Nonsense	[43]		2398delC	Frameshift	[24, 43]
	1189A>T	Missense	[69]		2399delG	Frameshift	[70]
	1212delC	Frameshift	[20, 38]		2440-1C>T	Splice site	[71]
	1225T>C	Missense	[20]		2440-6C>G	Splice site	[41]
	1285C>T	Missense	[45]	16	Del exon 16 (828 bp)	Truncation	[37]
	1306_1303insA, 1306_1307delTT	Frameshift	[72]				

Mutations with unknown pathogenic relevance, or identified in cancers other than DGC excluded

[a] Referenced in this paper

[b] Family does not meet HDGC criteria

ilies. The frequency of *CDH1* mutations in families that meet the International Gastric Cancer Linkage Consortium (IGCLC) criteria for HDGC (see below) appears to be inversely proportional to the incidence of GC in the general population from which the family is drawn, with countries with high incidence of GC having lower incidence of germline *CDH1* mutations identified in patients meeting the IGCLC testing criteria [40]. As yet, no genotype–phenotype correlations are apparent.

As per Knudson's two-hit hypothesis of tumour suppressor gene inactivation, a second event is required to account for loss or inactivation of the wild-type *CDH1* allele [73]. Promoter hypermethylation of the second *CDH1* allele has been demonstrated by several groups as the most common mechanism inactivating the wild-type *CDH1* allele in HDGC [42, 74]. *CDH1* promoter hypermethylation has been found in prostate, breast and sporadic GC [75, 76], and was demonstrated by Grady et al. in 2000 to be the "2nd hit" in some HDGC patients [77]. Grady et al. also demonstrated in vitro that the demethylating agent, 5-azacytidine restored E-cadherin expression in a GC cell line that tested positive for *CDH1* promoter methylation, revealing that methylation was the mechanism of silencing. Other mechanisms include somatic mutation, one case of an intragenic deletion has been identified, and it is thought that histone modifications may also be important [42, 68, 74, 78]. In GC tumours from HDGC patients', loss of heterozygosity is another mechanism for loss of the wild-type *CDH1* allele [12, 15, 19, 74].

It is not uncommon for HDGC patients to have multiple foci of tumour in their gastrectomy specimens. Genetic analysis of multiple tumours in the same individual reveal that different mechanisms of silencing of the second allele occur independently at multiple sites in metastatic deposits [74] and within lesions of the stomach [79] .

Non-CDH1 Hereditary Diffuse Gastric Cancer

About 25 to 30% of patients meeting current clinical criteria for HDGC are found to have germline mutations in *CDH1,* meaning that up to 70% of families have no identifiable mutation [7]. Using the nomenclature reported by Blair et al., families that fulfil the IGCLC criteria for HDGC (see below) but have no identified *CDH1* mutation are designated familial diffuse gastric cancer (FDGC), HDGC refers only to families with a pathogenic *CDH1* mutation [10]. *CDH1* genetic testing involves sequencing and multiplex ligation-dependent probe amplification (MLPA) to detect large deletions. While this testing is currently the gold standard, there may still be mutations that are missed due to technological limitations. Families without identified *CDH1* mutations have been investigated for other potential candidate genes involved in FDGC. In a Dutch kindred with FDGC, a mutation has recently been identified in *CTNNA1*, which encodes alpha-E-catenin, making this a potential causative mutation in FDGC [80]. Alpha-E-catenin, in a complex with beta-catenin, binds the cytoplasmic domain of E-cadherin to the cytoskeleton [32, 81, 82]. Loss of *CTNNA1* in animal models induces altered cell polarity, hyperproliferation, and increase in Ras- and mitogen-activated kinase (MAPK) activity—features which are consistent with the potential to induce a malignant phenotype [83]. While the *CTNNA1* mutation in this family is suspicious of pathogenicity for HDGC, the phenotype suggests older onset of DGC and mutations in *CTNNA1* have not been found in other families to validate the result. It is likely that some families with FDGC may harbour mutations in other genes that have yet to be identified.

Other Malignancies Associated with HDGC

Other malignancies have shown higher prevalence in families with HDGC, the most prominent of which is Lobular Breast Cancer (LBC) [10, 16, 18, 48]. The risk for developing LBC for females with *CDH1* mutations is approximately 60% by age 80 [7]. Therefore, LBC is considered a cancer in the HDGC syndrome that warrants specific management. Colorectal cancer has been

identified in some HDGC kindreds [19, 20, 41], although the numbers are small and given this is such a common cancer in the community, direct pathogenesis from a *CDH1* mutation has not been established [18].

Other Hereditary Syndromes Associated with Gastric Cancer

Other hereditary syndromes are associated with increased risk for GC, including Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC), hereditary breast and ovarian cancer, familial adenomatous polyposis (FAP), Cowdens syndrome and Peutz–Jeghers syndrome. Table 6.2 describes the associated risk of GC, which can be intestinal or diffuse type, with selected syndromes where it is known. Patients with hereditary breast and ovarian cancer syndrome have increased risks of malignancies in addition to breast and ovarian cancer, including gastric cancer although the risks are not well quantified [84, 85]. Patients with Lynch syndrome, in addition to colorectal cancer, are at risk of GC, other gastrointestinal malignancies, endometrial carcinoma and carcinomas of the renal tract [6, 86, 87].

Polyposis of the gastrointestinal (GI) tract is associated with a number of familial cancer syndromes. Upper GI polyposis is frequently found associated with FAP. In the stomach this is manifested as fundic gland polyposis [89, 90]. Although sporadic fundic gland polyps are considered to be non-neoplastic, in FAP patients some have been found to harbour dysplasia which may evolve into invasive GC [89, 91, 92]. Peutz–Jeghers and Cowden syndrome patients present with polyposis of multiple organs. Only rare cases of GC have been reported in Cowden syndrome, suggesting this is not a common manifestation of this disease [93, 94]. The risk of cancer in Peutz–Jeghers syndrome is higher, with a lifetime risk of GC of 29 % [88]. Juvenile polyposis syndrome is another syndrome associated with hamartomatous polyp formation of the GI tract, with associated increased risk of GI malignancy mainly related to colorectal cancer, but GC has also been documented [95, 96]. GC has also been seen in families with Li–Fraumeni syndrome [97, 98], and some FDGC families have been identified with *TP53* mutations suggesting GC is a component of Li–Fraumeni syndrome spectrum [57]. Although there appears to be no significant increase in the incidence of GC in patients with *MUTYH*-associated polyposis, a autosomal recessive disorder caused by germline mutations in the base excision repair gene *MUTYH* [99], monoallelic *MUTYH* mutation carriers have been reported to have a higher incidence of GC than the general population [100]. There are reports of an increased incidence of GC in relatives of patients with Fanconi's anaemia [101]. In 2012 a new autosomal dominant condition associated with gastric polyposis and intestinal GC was described. This featured proximal polyposis of the stomach and GC and was named gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) [102, 103]. The causative gene for this syndrome is unknown.

Table 6.2 Inherited cancer syndromes with associated GC risk

Cancer syndrome	Gene	Gastric cancer risk lifetime risk (%)	Ref.
HDGC	*CDH1*	80	[7]
Hereditary breast/ovarian cancer	*BRCA1*	5.5 (3.4–7.5)	[85]
	BRCA2	2.6 (1.5–4.6)	[84]
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*	4.4–19.3	[6, 87]
Peutz–Jeghers syndrome	*STKII*	29	[88]

Pathology

Mechanism of Tumorigenesis

E-cadherin is involved in cell adhesion, epithelial-to-mesenchymal transition (EMT) and in regulation of Wnt signalling via beta-catenin. Although the exact mechanisms by which loss of E-cadherin instigates tumorigenesis remain to be elucidated, it is thought that in HDGC, *CDH1* acts as a tumour suppressor gene, with loss of function leading to loss of cell adhesion with subsequent invasion and metastasis. One hypothesis is that loss of E-cadherin and subsequent loss of cell adhesion causes disruption to cell polarity that interferes with cell division and results in daughter cells being deposited in the lamina propria, which then expand forming foci of SRCs [78]. The in vitro and in vivo evidence available suggests that the loss of cell adhesion alone caused by deficient E-cadherin expression is sufficient to initiate DGC.

Loss of E-cadherin expression is one of the hallmarks of EMT [104]. EMT is the process by which epithelial cells assume a more mesenchymal phenotype, including the ability to migrate through the basement membrane and possess some resistance to apoptosis [105]. This process is normal in human development, but is pathological when implicated in tumour progression and metastasis. In addition to disrupting cell adhesion and therefore potentiating an invasive phenotype, loss of E-cadherin expression also promotes dysregulated beta-catenin signalling through the canonical Wnt signalling pathway which has been associated with tumorigenesis in a wide variety of cancers [106].

E-cadherin's role as a suppressor of tumour invasion has been shown in vitro, where loss of expression or function leads to altered cell phenotype and enhanced cell invasiveness [27]. This phenotype can be reverted by restoring E-cadherin protein expression after transfection of E-cadherin coding cDNA [107, 108].

The important role that E-cadherin has in embryogenesis is reflected in the fact that E-cadherin homozygous knockout mice are embryonic lethal [109]. Heterozygous mutant animals are phenotypically normal, and have been used to establish a mouse model of DGC by exposure to a carcinogen (*N*-methyl-*N*-nitrosurea) to induce the 2nd hit [79, 109]. It was noted that compared to wild-type treated mice, $Cdh1^{+/-}$ mice developed intramucosal SRCCs 11 times more frequently. In addition to loss of E-cadherin expression, the SRCCs showed a low proliferative activity and absence of nuclear beta catenin accumulation, suggesting that in the absence of increased proliferation or Wnt signalling activation, loss of cell-to-cell adhesion alone was sufficient to initiate a DGC in these models [79]. This is consistent with the clinical observation, where hundreds of independent foci of SRCCs can occur in the stomachs of patients with germline *CDH1* mutations, which suggests that it is unlikely that other genes are required to initiate HDGC [78].

It is not known why germline *CDH1* mutations predispose to DGC, and LBC, but not significantly to other malignancies. One hypothesis is the higher carcinogen exposure and chronic inflammation that the gastric epithelium is exposed to, another is the high cellular turnover of the gastric epithelium [78]. In these settings, fewer mutational or epigenetic events may be required to generate an invasive malignant phenotype. It is notable, however, that epithelial cell turnover in the intestine is also high, and why colorectal cancer is not more apparent in patients with *CDH1* mutations remains unresolved.

Risk Modifiers

There has not been a comprehensive analysis of the genetic or environmental factors that impact on penetrance of HDGC. Knowledge of these would be beneficial for genetic counselling on risk behaviours and on genetic risk profile. However, there are a number of lifestyle and environmental factors that have been identified to impact on risk of sporadic GC (see Chaps. 1–3), and it is possible that these factors may also impact on HDGC.

Helicobacter Pylori

Helicobacter pylori (*H. pylori*) was classified as a class I carcinogen by the World Health

Organisation in 1994, and has a well-established association with GC [110]. It has been implicated in both sporadic intestinal GC, and DGC, and although it does not appear to be required for oncogenesis in HDGC [66, 111–113], it theoretically may modulate disease risk [114]. Current recommendations for HDGC suggest eradicating *H. pylori* if found [10], but there are no prospective analyses showing impact of this on progression of HDGC.

Physical Activity and Diet

Numerous studies have investigated the association of sporadic GC with demographics, diet and physical activity; however, there are no studies that investigate HDGC specifically or as a subgroup.

Diet and food storage have been implicated in the changing incidence of sporadic GC, with the adoption of refrigeration improving access to fresh fruit and vegetables and reducing the need for salt preservation of food being implicated in the decrease in incidence observed in GC [115–118]. The European Prospective Investigation into Cancer and Nutrition (EPIC) study was designed to prospectively investigate relationships between cancer incidence and lifestyle, genetic and environmental factors. It found an inverse association with vegetable intake for intestinal GC, but not diffuse GC, and no association with fruit intake [119]. For sporadic GC, the EPIC study demonstrated an inverse association with physical activity, particularly in non-cardiac GC [120]. Findings of the EPIC study also showed an association between smoking and sporadic GC, with approximately 18% of cases in this study being attributable to smoking [121]. Whether smoking, physical activity, diet or other environmental factors impact on the penetrance of HDGC is unknown, but would be assumed to have similar affects as in sporadic GC.

CDH1 Mutations in Sporadic GC

E-cadherin gene mutations were identified in sporadic GC prior to the identification of *CDH1* as the gene responsible for HDGC [29]. Inactivating somatic mutations in *CDH1* are detected in over 50% of sporadic DGC, but not intestinal GC [29, 122]. As with HDGC, promoter methylation of *CDH1* has been identified in sporadic DGC as the 2nd hit [122]. The high prevalence of mutation and epigenetic silencing of *CDH1* suggests that the inactivation of E-cadherin has a role in the evolution of sporadic DGC as well as HDGC, with the earlier age of onset of GC seen in HDGC kindreds reflecting the fact that only one wild-type *CDH1* allele requires mutation to develop a potentially malignant genotype. Interestingly, although mutations in *CDH1* are not seen in intestinal GC, promoter methylation has been identified in a subset of intestinal GC [76, 122]. It is likely that silencing of E-cadherin expression has an effect on the later stages of the carcinogenic cascade in intestinal type GCs, whereas it has a role in early pathogenesis of DGC.

Management of HDGC

Clinical Criteria for Genetic Testing

Figure 6.1 describes the suggested process for the diagnosis and management of HDGC. The most recent published guidelines for determining which individuals to test for *CDH1* mutations from the IGCLC were published in 2010 [7]. They recommend genetic testing for patients who meet the following criteria:

- Two or more GC cases in one family, with one confirmed DGC before 50 years of age
- Three or more confirmed DGC cases in 1st or 2nd degree relatives, independent of age of onset
- DGC in individual less than 40 years of age regardless of family history
- Personal or family history of DGC and LBC, one diagnosed before 50 years of age

It is expected that these guidelines will be updated in 2015 and may provide changes in the inclusion criteria. In addition to the above guidelines, the IGCLC recommends consideration to offering genetic testing to patients where pathologists identify in situ SRCs or pagetoid spread of SRCs adjacent to DGC, as this is rarely seen in sporadic DGC [123].

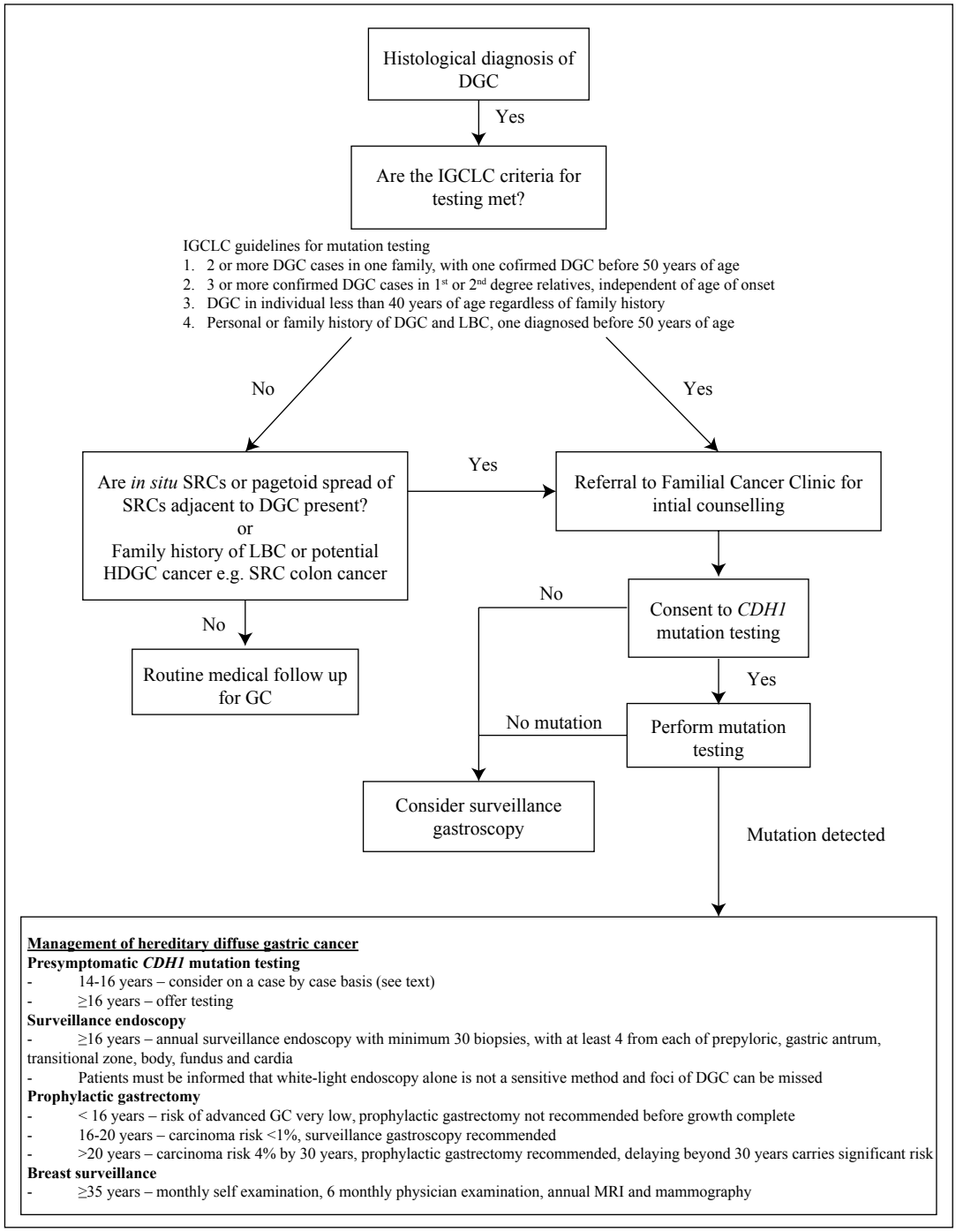

Fig. 6.1 Flow chart for diagnosis and management of HDGC. (Modified from Blair et al. 2006 [10])

Using the older IGCLC guidelines, which were more restrictive, to determine which families to screen, the detection rate of *CDH1* mutations was between 25 and 50% [14, 20, 24, 45, 124]. Mutations have been found in individuals from kindreds who do not meet the 2010 IGCLC

criteria, and it has been suggested that recommendations for testing also include families with multiple cases of early onset LBC in the absence of DGC [43]. Because of the inverse relationship seen between *CDH1* mutations and the incidence of GC geographically, families from geographic areas with a high prevalence of sporadic GC are less likely to return a positive result on mutation testing than those from geographic areas of low incidence [40]. The clinical decision whether to screen for a *CDH1* mutation therefore needs to take into account the risk of GC for the population from which the patient and family is derived, in addition to the family and personal history of GC and other cancers.

Genetic Testing

Once a patient or family has been identified as being at risk of carrying a *CDH1* mutation, a full genetic assessment needs to be carried out, and requires referral to an appropriate genetic service. A careful, at least, three-generation family pedigree should be obtained, and confirmation of DGC diagnoses should be obtained [7]. If criteria for testing are met, formal genetic counselling and consent for genetic testing should be offered. The consultation with an expert in HDGC will provide information of the natural history of GC, the definitions of HDGC, and discussion on the concepts of autosomal dominant inheritance and incomplete penetrance. If a pathogenic mutation is identified in the proband then predictive testing for family members deemed at risk will be offered. Appropriate genetic counselling will cover issues such as the implications of a positive test result on impacts on health and life insurance and also future management of carriers of a *CDH1* mutation. Psychological support can be provided throughout the testing and counselling process because of the uncertainty associated with an incompletely penetrant disorder, the implications of positive and negative results, and the distress that can be associated with this [125, 126].

Genetic testing is performed on blood from an affected family member [126]. If blood is not available DNA of an affected individual from an archived paraffin block can also be used although this testing has technical challenges [126]. There are no hot spots in the gene to target, hence, the entire coding sequence of the gene including intron–exon boundaries needs to be examined for mutation [24]. As mentioned genetic testing involves sequencing and MLPA due to the finding of large intragenic deletions in families [8, 37].

It is unclear from current evidence at what age family members at risk of harbouring *CDH1* mutations should be offered genetic testing given the risk of malignancy is low before the age of 20 [18, 24], however some carriers have developed overt cancer prior to the age of 18 [12, 16]. The IGCLC recommends testing be considered from the age of consent, which will vary by country. This will be partly dependent on the age of diagnosis of the earliest cancer in the family. Psychological, physical and emotional health of the individual in question and their family also need to be taken into account in the timing of genetic testing [7].

Management of a CDH1 Mutation Carrier

This should be carried out through a multidisciplinary team that includes but is not limited to a genetic counsellor, geneticist, gastroenterologist, surgeon, dietician and psychologist. Patients are counselled to have a prophylactic gastrectomy at the earliest achievable time. Given the high penetrance of disease and variable natural history of disease this is usually recommended for mutation carriers in their early 20s. Some patients prefer to delay gastrectomy and the only other option is endoscopic surveillance although there are significant deficiencies in this methodology at this point in time.

Surveillance

Early GC in HDGC usually consists of small foci of SRCs, which are usually submillimetre, intramucosal and multifocal, making it difficult to identify at routine white light endoscopy (Fig. 6.2). Case reports exist of patients who have presented with extensive DGC despite normal

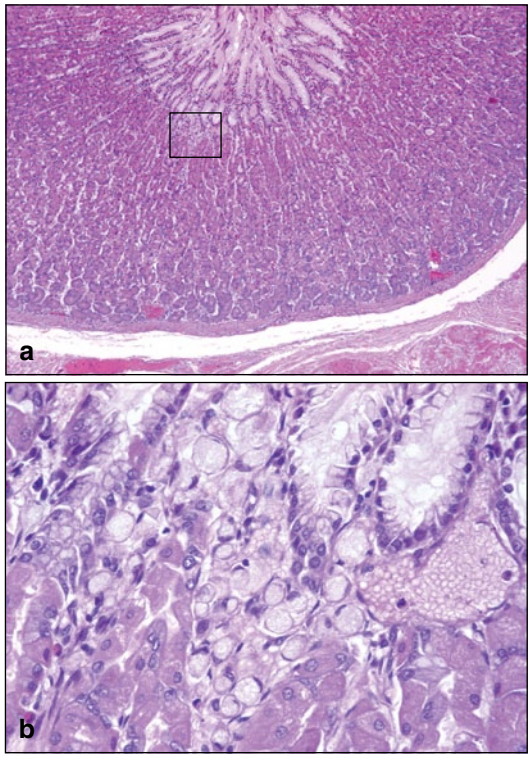

Fig. 6.2 Signet ring cells (SRCs) with 0.3 mm mucosal focus found at prophylactic gastrectomy in a *CDH1* mutation carrier (female, 26). **a** Low power view (H&E 50x) and **b** high power view (H&E 400x) of boxed area

endoscopy with negative biopsies [113]. Multiple groups have also published series of patients undergoing prophylactic gastrectomy for *CDH1* mutations, who despite normal investigations presurgery had multiple independent foci of T1a SRCC identified at pathological assessment [8, 45, 55, 66, 70, 112, 113, 127].

Current recommendations for endoscopic surveillance in patients with mutation who decline prophylactic gastrectomy, or who are less than 20 years of age, suggest that this should be performed under a research protocol if at all possible to allow evaluation of new endoscopic modalities and to allow investigation of the natural history of HDGC [7]. Endoscopy should be performed at least annually to investigate any clinically significant lesions, ideally at a centre with experience with HDGC. The entire gastric mucosa should be inspected and photographed and any suspicious lesion should be biopsied. In addition, a minimum of 30 random biopsies is recommended from the different anatomic areas of the stomach. These include: prepyloric, antrum, transitional zone, body, fundus and cardia to maximise the likelihood of finding microscopic foci of SRCs [7]. Patients should be made aware that because of the small size and multifocal nature of early SRC lesions it is likely that early lesions will not be detected by random biopsies.

There is a reported propensity of SRCC lesions at the antral–corpus or body–antral junction but this has not been independently validated. Charlton et al. examined six gastrectomy specimens and reported that the distal third of the stomach contained 48% of total foci [66]. The body–antral transitional zone, which occupied 7.7% of the mucosal area, contained 37% foci, and had the largest foci. They concluded that targeting the transition zone would maximise the likelihood of finding microscopic foci of SRCs in HDGC patients. This has not been replicated in other studies. Carniero et al. found no anatomical clustering in nine gastrectomy specimens [111]. Rogers et al. and Barber et al. examining eight gastrectomy specimens each noted a higher prevalence of foci of SRCs in the proximal stomach [49, 127]. As yet the reasons behind the different anatomical clustering of lesions have not been identified, and may represent the different ethnic and geographic origins of the patients, and differing environmental exposures. On the basis of current evidence, anatomical targeting of otherwise normal mucosa cannot be recommended; hence multiple biopsies of all areas of the stomach are suggested in addition to targeted biopsies of obvious lesions.

Chromoendoscopic techniques have also been trialled as a method of improving endoscopic surveillance. Using a methylene blue and congo red technique Shaw et al. were able to identify foci of carcinoma >4 mm not visualised on white light endoscopy [128]. These results have not been replicated in another study [50], and due to concerns of carcinogenic potential of both congo red and methylene blue these are not recommended [129, 130]. At this time chromoendoscopy cannot be recommended outside a clinical trial.

Positron emission tomography (PET) has been investigated as a potential surveillance method. In one case report fluoro-2-deoxy-D-glucose (FDG)-PET was able to identify early GC in an asymptomatic *CDH1* mutation carrier [131]. This has not been replicated in other studies, with reports of patients with negative FDG-PET scans harbouring foci of malignancy at pathological review [8, 24]. Currently no imaging technique is satisfactory for surveillance in HDGC, and should only be included in a research protocol.

The best surveillance includes careful endoscopic examination of the stomach with insufflation and suction of the stomach to ensure no linitus plastica with both targeted and random biopsies of regions representing the entire stomach.

Prophylactic Total Gastrectomy

Patients who develop symptomatic DGC have a poor 5 year survival of approximately 10% despite current treatments, with the majority dying before the age of 40 [132]. In view of the poor survival once symptomatic and the lack of effective surveillance for mutation carriers, prophylactic gastrectomy is recommended to all mutation carriers. As noted above, although performed with prophylactic intent, most published series find foci of DGC or SRCC in gastrectomy specimens, even in those patients who have undergone extensive presurgical screening, however most show only T1N0 disease [8, 45, 55, 66, 70, 112, 113, 127]. Preoperatively all patients should undergo endoscopy to exclude gross abnormalities, have random biopsies performed and to delineate the gastro–oesophageal junction [126]. CT of the abdomen to exclude lymphadenopathy or other disease in otherwise young patients is not always necessary.

The below discussion is specific to prophylactic gastrectomy and not gastrectomy for established GC (for a discussion on gastrectomy and postoperative management see Part III: Gastric resection and postoperative management). Gastrectomy for HDGC should be performed in a centre with expertise in the surgery and low operative mortality. Gastrectomy must be total, as SRCs can be found throughout the entire stomach and any remnant stomach would maintain the risk for DGC. The proximal resection margin must transect the oesophagus to ensure no gastric mucosa is left behind [133, 134]. In the prophylactic setting, D2 nodal dissection is not necessary as no lymph node metastases have yet been observed, therefore only lymph nodes harvested during the gastric resection should be removed [7, 135]. Currently Roux-en-Y reconstruction in an open procedure should be standard. Any surgeon proposing laparoscopic prophylactic gastrectomy, or alternative surgical reconstruction must be able to reassure the patient with audited data that this does not involve additional risk [7].

Patients need to be counselled about the short- and long-term morbidity and mortality of gastrectomy. This is part of the function of the multidisciplinary team, including genetic counsellor, psychologist, gastroenterologist, gastric surgeon, dietician and specialist nurse. It may also be helpful for patients to discuss the procedure with other individuals who have had the same operation. The early and late complications of gastric resection are documented in detail in Chaps. 20 and 22. In the setting of HDGC and prophylactic gastrectomy, it must be remembered that patients undergoing this procedure are likely to be significantly younger than patients undergoing gastrectomy for sporadic GC, and therefore the long-term consequences of morbidity from the procedure may be different, and potentially greater. In the prophylactic setting mortality from gastrectomy should be no more than 1% [10]. In addition to the mortality risk, patients must be informed about potential operative complications including haemorrhage, anastomotic leak and/or stricture and anaesthetic complications [126]. The long-term morbidity from total gastrectomy is substantial but often transient with 100% of patients experiencing a variable degree of weight loss, alteration in eating habits, dumping syndrome and nutritional deficiencies in vitamin B_{12}, iron, thiamine and zinc [44]. These must be discussed and managed, emphasising the importance of a dietician. After surgery physical function usually returns to normal by approximately 6 months [7]. Psychological aspects of gastrectomy

can have a profound effect on individuals particularly on the issue of body image that may need specific psychological input.

One concern that may affect the timing of prophylactic gastrectomy in female mutation carriers is the preservation of fertility. Patients may wish to postpone gastrectomy until after childbearing is complete. However, there are reports of successful pregnancy following prophylactic gastrectomy for HDGC [136], and after gastrectomy for other reasons [137, 138]. Maternal anaemia was the only significant complication potentially related to the previous gastrectomy, and appropriate monitoring and supplementation for nutritional deficiencies is recommended [136] .

The optimal timing of prophylactic gastrectomy is unknown. However, in most kindreds it is thought the risk of GC before age 20 is less than 1 %, and therefore, the mortality risk from the surgery is higher than the risk reduction from surgery before the age of 20 [10]. At present, consensus recommendations are for surgery to occur after the age of 20, although the earliest onset of GC in each family must be considered [7]. There is no absolute contraindication to prophylactic total gastrectomy in the setting of HDGC.

The importance of comprehensive pathological review of the gastrectomy specimen cannot be understated. This is shown by the publication of a case initially reported as showing non-penetrance, and the discussion of publication bias accounting for lack of similar cases being published [139, 140]. The specimen was subsequently reviewed in more detail and four foci of intramucosal carcinoma and three foci of in situ carcinoma were identified [139]. Processing and reporting of gastrectomy specimens should follow specific guidelines, including full specimen photography to allow for accurate mapping of any foci of carcinoma. Figure 6.3 shows a gastrectomy specimen with the location of invasive foci of SRCs identified. The pathology report should document status of the margins, any features of invasive carcinoma including site, histological subtype, lymphatic, venous or neural invasion, precursor lesions, and features of the non-neoplastic mucosa, including *H. pylori*, intestinal metaplasia, and gastritis [7]. If there are lymph nodes in the specimen, they should also

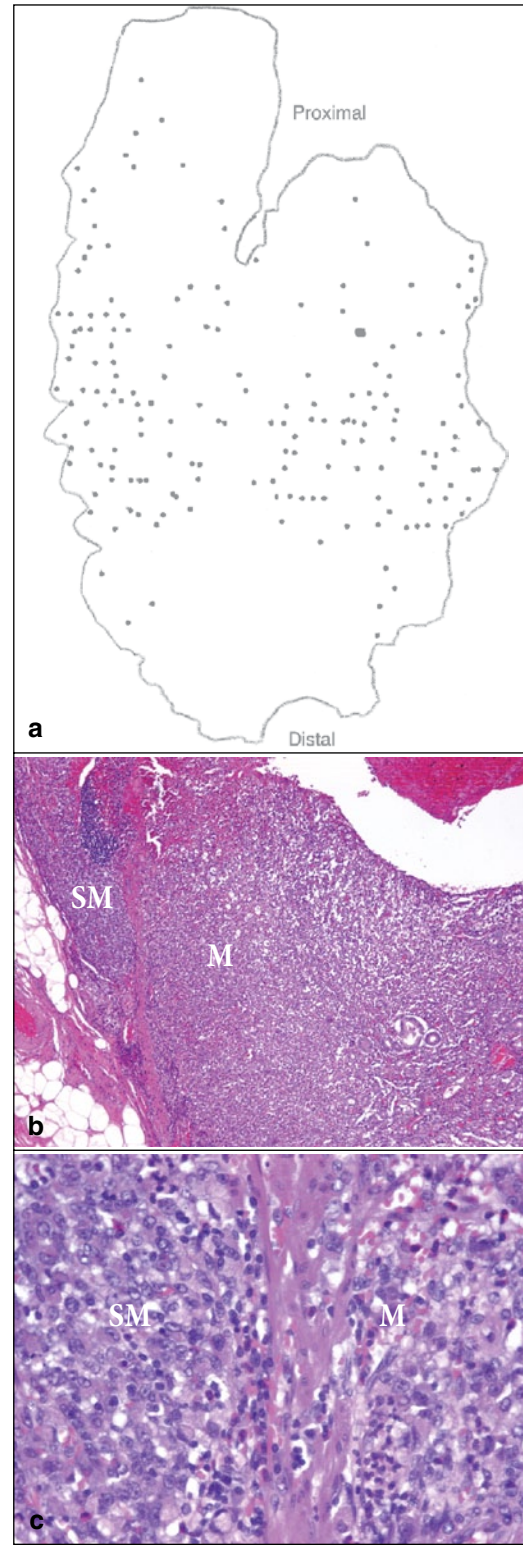

Fig. 6.3 Prophylactic gastrectomy specimen from a *CDH1* mutation carrier (female, 22). **a** Stomach map

be sampled. If the entire stomach is not sampled, and no evidence of carcinoma is found, this should be reported as no carcinoma found in the proportion of mucosa examined, not negative for carcinoma [7].

Follow-up postgastrectomy is essential to monitor for nutritional deficiencies or other late presenting side effects [134].

Breast Cancer Surveillance

The cumulative lifetime risk of LBC for female *CDH1* mutation carriers is thought to be 60 % by age 80 [7]. Screening for breast cancer is recommended to begin at age 35, although the exact age that risk starts increasing is unknown. Screening for LBC should include monthly self-examinations, 6th monthly examinations by a physician and annual mammography and MRI from the age of 35 [7, 18, 134]. MRI is recommended as lobular breast cancer may be missed on mammogram [141]. Prophylactic mastectomy has been performed in some women with *CDH1* mutations, but its role in HDGC is still uncertain [48, 142]. Most LBCs are oestrogen receptor positive, but there is insufficient evidence to recommend chemoprevention with tamoxifen as yet [7, 142] .

Knowledge Gaps

Our understanding of the biology of HDGC has significant gaps that impact on the management of patients. A better understanding of the additional factors that influence penetrance, both environmental and genetic, will help in determining which patients require total gastrectomy and the timing of gastrectomy. Understanding the rate of progression of SRCC to DGC would have implications for timing of surgery for patients but at this point it appears quite variable from patient to patient.

Current methods for surveillance for GC are insensitive, necessitating prophylactic gastrectomy in asymptomatic patients. Improved surveillance methods may allow for gastrectomy to be postponed, thereby postponing the morbidity and mortality risk associated with the procedure. In addition, for LBC, the information available to guide surveillance, potential chemotherapeutic strategies, and the utility of surgical prophylaxis is limited. These are all areas where improved knowledge has potential in alter patient treatment and outcome. Equally, the knowledge on risks of other cancers, in particular colorectal cancer, in HDGC is limited. Therefore, it is unknown whether screening for extra-gastric malignancies, in particular colorectal cancer, needs to be more intensive in HDGC families than what is offered to the general population.

Summary

HDGC is a rare condition that has significant implications for individuals and families affected. Optimal management of gene mutation carriers requires an experienced multidisciplinary team to undertake diagnosis, genetic counselling, surgery and postoperative management. Because of the multiple areas where knowledge is incomplete, ongoing research to improve patient management is imperative.

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diagram demonstrating location of foci of invasive signet ring cells (SRCs) within mucosa (M), *large dot* represents 10 mm focus with invasion into submucosa (SM). **b** Low power (H&E 50x). **c** High power (H&E 400x)

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Western Perspective and Epidemiology of Gastric Cancer

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Epidemiology of Gastric Cancer in Western Countries

There is a wide geographical variation in gastric cancer incidence with remarkable differences between Eastern and Western countries. In 2012, 58% (552,935/951,594) of new cases of gastric cancer occurred in Eastern Asia, mainly in China. There are more new cases of gastric cancer in Japan (107,898 in 2012) than in the 28 countries of the European Union (81,592), or in South Korea (31,269) than in the entire USA (21,155) [1].

As shown in Fig. 7.1, age-standardized incidence rates are the highest in South Korea (62.3 per 100,000 person-years in men and 24.7 in women) and Japan (45.8 and 16.5 per 100,000, respectively) and the lowest in North America (in the USA 5.3 and 2.7 per 100,000 person-years, respectively).

Large differences in incidence exist also within the same continent: for instance, within Europe, gastric cancer incidence varies four to fivefold, being particularly high in Eastern Countries (24.5 and 10.8 per 100,000 person-years in Russian men and women) and particularly low in Scandinavia (4.9 and 2.7 per 100,000 person-years in Swedish men and women). Likewise, in South America, incidence is much higher on the Pacific coast than in countries facing the Atlantic Ocean.

Gastric cancer is the third leading cause of cancer death worldwide. The pattern of mortality largely reflects the pattern of incidence, being the highest in Eastern Asia and the lowest in North America. At variance mortality is higher in China (25.5 and 10.7 per 100,000 person-years in men and women) than in South Korea (19.6 and 7.9 per 100,000 person-years), where incidence is nevertheless twofold higher. Indeed the ratio of deceased to incident cases varies largely worldwide, being as low as 34.4% in South Korea, close to 50% in Japan (48.5%) and USA (55.6%), 71.6% in the European Union and 80.3% in China in 2012. In most developing countries mortality rate approaches incidence rate. (Of note, to compare mortality and incidence within the same country, we did not use standardized rates that, using as reference the world population, would

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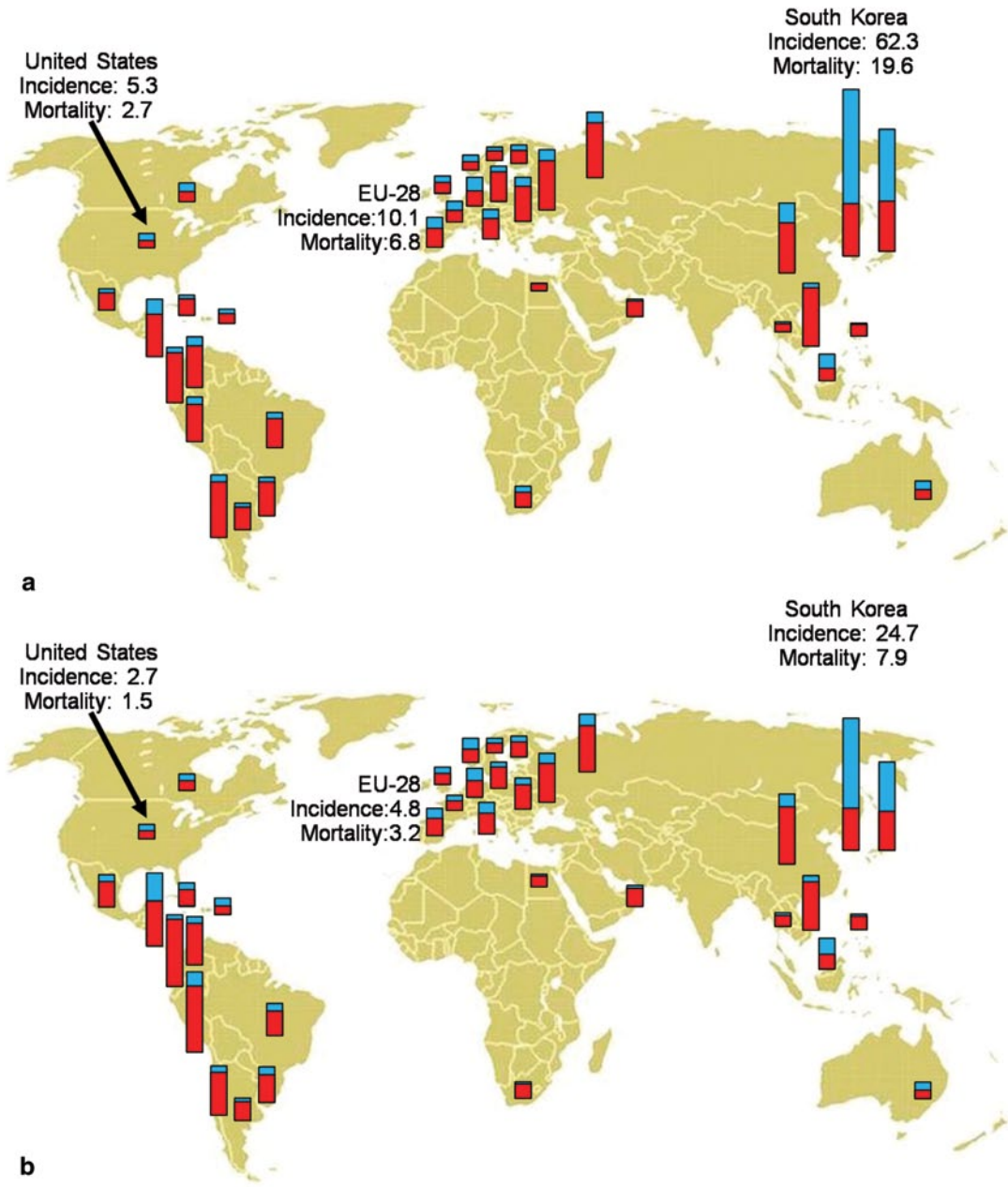

Fig. 7.1 Age-standardized incidence (*blue* + *red* columns) and mortality (*red* columns) from gastric cancer in 2012 in men **a** and women **b** (GLOBOCAN 2012). Only countries with at least score E for availability of incidence data and score 4 for availability of mortality data were included. Some European data were not reported to avoid column superimposition

have attributed larger weights to incidence than to mortality. Direct standardization was instead mandatory when comparing incidence and mortality across different countries, as in Fig. 7.1.)

Over the last 30-year period, there has been a marked decline in age-standardized incidence and mortality from gastric cancer, which involved almost all populations: from 2000–2004

to 2005–2009 mortality from gastric cancer among men declined by 26% in South Korea, by 15% in Japan, by 17% in the European Union and by 15% in the USA [2]. Similar changes were observed in women.

A decrease in the rate of infection with *Helicobacter pylori* is the most important factor contributing to the reduced stomach cancer burden worldwide [3]. The decrease in incidence is partly counteracted by population ageing.

Clinico-Pathological Characteristics in Western Countries

The declining incidence in stomach cancer throughout the world is mostly attributed to a fall in incidence of distal, intestinal type tumours, which correlates with the decreasing prevalence of *H. pylori* infection [4]. As the large variability in gastric cancer incidence between high- and low-incidence countries mainly reflects a large discrepancy in new cases of intestinal distal cancer, there is currently a higher proportion of cardia, proximal and diffuse-type gastric cancer, especially signet ring cell (SRC) [5], in countries with lower incidence and mortality rates of stomach cancer.

Indeed in contrast to adenocarcinoma of the distal oesophagus, which has increased markedly, the literature on temporal trends of cardia and proximal gastric cancer is somewhat conflicting, with decreasing, stable and increasing incidence rates reported [6–10]. However, considering the steep declining of intestinal distal type, the proportions of cardia and proximal tumours have been increasing over the last decade in almost all populations [11–15].

A recent report [2] highlights that the contribution from the cardia as a proportion of the total gastric cancer incidence varies as a function of gastric cancer incidence, being the lowest in South Korea (5.8% in men and 4.3% in women) and the highest in Northern Europe (72% in Finnish men and 44.5% in British women). Indeed, cardia cancer exceeds non-cardia cancer in several male populations of Northern (Finland, Denmark, UK) and Central Europe (Belgium, Austria). Moreover, a proportion close to 50% is observed in men of most Anglosaxon countries (USA, Canada, Australia, New Zealand).

At variance with intestinal-type gastric cancer, the incidence of diffuse gastric cancer, particularly the SRC type, has been increasing and nowadays represents a great proportion of stomach tumours in Western series. When analyzing the Surveillance Epidemiology and End Results (SEER) database using the Lauren classification, the intestinal histotype decreased by 52% from 1973 through 2000 (on average 2.4% per year), while the diffuse histotype increased by 441% in the same time period (3.6% per year). The highest rise was observed for the SRC type which increased by 6.5% per year, i.e. by 998% from 1973 to 2000 [5]. Thereafter, a decreasing trend has been found for absolute diffuse cases, which is probably related to changes in coding procedures [14], while the ratio of diffuse compared to intestinal histotype is still increasing, especially for non-cardia gastric cancer.

Different epidemiological trends strengthen the hypothesis that proximal intestinal, distal intestinal and diffuse subtypes of gastric cancer may be distinct diseases, related to different risk factors and thus characterized by different biological behaviour.

It is interesting to note that recent Western reports [16], including a GIRCG (Italian Research Group for Gastric Cancer) clinical study on temporal trends [10], show no improving or even worsening prognosis in recent years, despite the enhanced clinical, surgical and oncological quality. These findings may be due to the above-mentioned changes in clinico-pathological features of gastric cancer: distal intestinal tumours, which are declining in Western countries, present the most favourable prognosis. Accordingly, Dutch and French epidemiological studies reported a clear-cut increase in the frequency of gastric *linitis plastica* and metastatic forms [17, 18], while in an Italian study the rate of peritoneal recurrence showed a progressive increase after radical surgery, with respect to locoregional or hematogenous spread [10].

Due to these epidemiological trends and the lack of screening programs, in the Western world

at least 70% of gastric cancers are diagnosed in advanced stages [10, 17, 19].

Western Surgical Approach: Historical Perspective

The large difference in gastric cancer incidence is one of the main reasons of the remarkable discrepancies in treatment strategies between Eastern and Western countries [20].

The extent of lymphadenectomy has been the most debated issue in gastric cancer surgery. Indeed, Japanese surgeons have routinely performed extended lymphadenectomies since decades, while Western surgeons preferred limited nodal dissections.

Western approach to advanced gastric cancer was largely influenced by the results of two randomized clinical trials (RCT), the UK Medical Research Council and Dutch Gastric Cancer trials [21, 22], reporting that D2 provided no 5-year survival advantage with respect to D1. Of note, the two trials had been carried out by surgeons without previous training in extended lymphadenectomy, with a surgical volume of less than five procedures per year. The limited surgical experience yielded a very high postoperative mortality after D2 dissection (9.7% in the Dutch trial and 13.5% in the British trial), probably related to the high percentage of splenectomies (37 and 65%, respectively) and pancreatectomies (30 and 56%) [23].

A Cochrane review, published in 2003 and 2005 [24, 25], taking into account the results of the above mentioned Western RCT concluded that extended lymphadenectomy does not offer survival benefits. However, the authors stated that "their results could be confounded by surgical learning curve and poor surgical compliance".

Despite of evidence-based indications, D2 lymphadenectomy has been routinely performed in the last two decades in high-volume Western centres. D2 lymphadenectomy is currently considered the standard of surgical treatment with curative intent by the German [26, 27] and British [28] national guidelines, the European Society for Medical Oncology (ESMO) guidelines [29], the joint ESMO—ESSO (European Society of Surgical Oncology—ESTRO (European Society of Radiotherapy and Oncology) guidelines [30] and the Italian Society of Surgery (SIC)-GIRGC guidelines [31]. At variance American NCCN guidelines recommend a D1+ or a modified D2 lymph node dissection [32].

Indexes of Surgical Quality in Gastric Cancer Surgery

In a previous study [33], we proposed as indexes of surgical quality the number of retrieved nodes, the percentage of splenectomy and distal pancreasectomy, the rate of postoperative complications and mortality. These indexes vary widely between the East and the West, probably as a function of surgeons' experience.

Indeed, extended lymphadenectomies were associated with a high number of harvested lymph nodes (median 39–54) and with a low (0.8%) or even absent postoperative mortality in Eastern trials [34, 35]. Conversely, in the Dutch and British clinical trials, D2 lymphadenectomy was associated with a lower number of retrieved lymph nodes and to a high postoperative mortality (10–13%) [21, 22].

In Western observational studies, indexes of surgical quality were intermediate between Eastern and European trials. Indeed in a GIRCG series, D2 lymphadenectomy was safely performed with a median number of harvested nodes of 29 and an adequate lymphadenectomy (>15 lymph nodes) achieved in 94% of cases [33].

In the recent years, it has been acknowledged that the unsatisfactory short-term results of the British and Dutch trials could have been avoided with an adequate training of participating surgeons. Indeed a more recent Western trial [36] comparing D1 and D2 lymphadenectomy, preceded by a phase 2 trial and including only experienced surgeons, presented a mortality of 2.2% after D2 dissections, further supporting that extended lymphadenectomy is a safe therapeutic option also in Western patients.

The quality of the surgical procedure surely affects short-term results, but can also influence

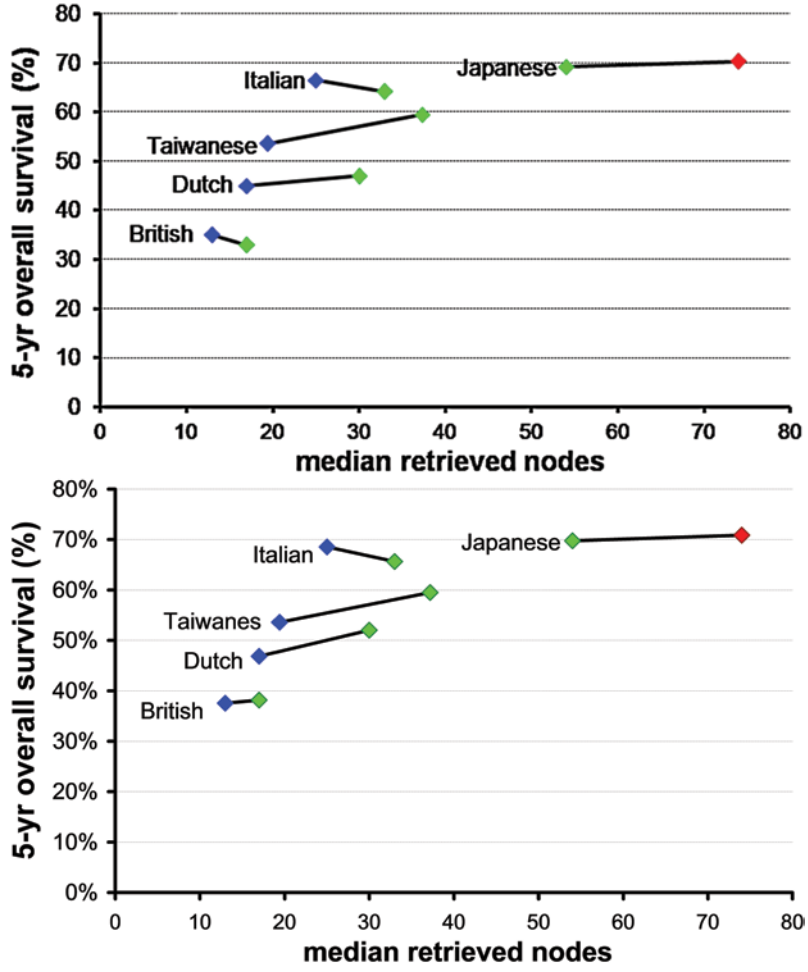

Fig. 7.2 Five-year overall survival as a function of median retrieved nodes in five clinical trials. *Four* trials (British, Dutch, Taiwanese, Italian) compared D1 (*blue diamonds*) and D2 (*green diamonds*), while the Japanese trial compared D2 and D2+PAND (*red diamond*). *Panel A*: whole series. *Panel B*: Patients dying in the postoperative period were excluded. *PAND* para-aortic nodal dissection

long-term survival. In Fig. 7.2, long-term survival of the most important RCTs [21, 22, 37–39] dealing with the extension of lymphadenectomy is presented as a function of the number of retrieved lymph nodes. When the trials are separately considered, discordant trends are apparent (panel A). After excluding patients dying in-hospital (panel B), an improvement in survival becomes clearly apparent when the more extended procedure allows to retrieve > 10 lymph nodes than the other procedure. No survival advantage is observed when > 50 nodes are detected also with the more limited procedure. If the five trials are considered together, 5-year overall survival seems to increase as a function of retrieved nodes reaching a plateau around 25–30 retrieved nodes. In addition, in the Italian trial, the high proportion (33 %) of early gastric cancer (pT1) can partly explain the lack of benefit after the D2 procedure [40].

This new perspective on the results of the most recent trials, based on the number of retrieved nodes rather than the planned extension of lymphadenectomy, further supports the central role of D2 lymphadenectomy in gastric cancer surgery, when performed by experienced surgeons.

Table 7.1 Five-year survival by stages in Eastern and high-volume Western series reported in the literature according to 7th TNM

	Ia (%)	Ib (%)	IIa (%)	IIb (%)	IIIa (%)	IIIb (%)	IIIc (%)
Kikuchi et al. [49]	–	94.30	84.80	71.30	64.8	48	23.1
Ahn et al. [48]	95.1	88.40	84	71.70	58.4	41.3	26.1
Marrelli et al. (GIRCG) [47]	97	89	86	69.00	59	35	11
Grabsch et al. [50]	81	58.00	55	35.00	32	13	10
Warneke et al. [51]	64	41	34	21	16	6	5

Marrelli [47] considered only deaths from gastric cancer progression, while the other studies [49–51] considered overall mortality. In [48, 49] post-operative deaths were excluded. In the study by Warneke, 5-yr survival was approximately computed from Fig. 2B of [51].

Some authors [41] pointed out that in the USA, the low volume of gastrectomies is the main obstacle in implementing extended lymphadenectomies, indeed in the USA, 80% of medicare patients undergo gastrectomy in centres performing less than 20 procedures per year [42]. That is the reason why NCCN Guidelines still include D1 resection as an acceptable procedure, but request a minimum of 15 dissected lymph nodes [32].

In Europe, many efforts are ongoing to increase the number of D2 dissections according to the above-mentioned guidelines, and centralization seems to be crucial in this context. Indeed in the Netherlands, survival of gastric cancer patients significantly improved after the implementation of the Dutch D1-D2 Gastric Cancer trial, which involved substantial standardization and training [43]. In Denmark, 30-day hospital mortality has decreased from 8.2 to 2.4% after centralization of gastric cancer surgery and implementation of national clinical guidelines while the proportion of patients with at least 15 lymph nodes removed has increased from 19 to 76% [44]. Centralization of gastric cancer surgery and/or audits for gastric cancer are currently implemented in UK, Sweden, Finland and the Netherlands [45, 46].

Survival Outcomes: West Still Differs from the East

As reported above, specialized high-volume Western centres currently provide high quality standardized surgical management of gastric cancer patients [33]. In GIRCG centres, [47] survival rates are very high and similar to Eastern series [48, 49], particularly in stages I and II, although in more advanced stages (IIIB and IIIC) lower survival rates than Eastern series are observed. However, even if there are some differences in series characteristics and survival end-points in papers reporting survival according to 7° TNM classification [49–51], long-term outcomes reported in other Western series [50–51] are remarkably worse than in Eastern series at each stage (Table 7.1).

Strong et al. [52] compared two high-volumes centres in USA and South Korea using an internationally validated nomogram, and found better survival for Korean patients. The reasons why survival in gastric cancer patients remains worse in the West despite improvements in surgical quality are not fully understood yet. Tentative explanations could be the following:

Differences in clinico-pathological features of gastric cancer in Eastern and Western countries could partially be responsible of the different outcomes. As already discussed, in low-incidence countries proximal and diffuse types are currently the most frequent subtypes of gastric cancer.

In many series [53–55], location of tumour in the proximal third has been shown to be an independent negative prognostic factor. The worse prognosis of proximal tumours has been explained by the more advanced stage, the larger size and the poorly differentiated histology, which are typical of this subtype of gastric cancer [56].

The real association between hystotype and survival of patients with gastric cancer is controversial. Indeed the prognostic significance of histology usually disappears after controlling for pTNM. It should be reminded, however, that Lauren diffuse cancers are more prone to give lymph node metastases; hence, stating that

Table 7.2 Five-year survival by depth of tumour invasion (7th TNM) in a single Eastern and high-volume Western centres

	pT1 (%)	pT2 (%)	pT3 (%)	pT4a (%)	pT4b (%)
Ahn et al. [48]	94.1	81.6	61.1	42.6	17.9
Marrelli et al. (GIRCG) [47]	94.8	77.7	60.0	30.3	10.4

Marrelli [47] considered only deaths from gastric cancer progression.

Lauren histotype is not an independent prognostic factor when adjusting for N status is not correct, as N status is not a confounder but rather an intermediate step in the causal pathway. In the Verona series, Lauren histology was an independent prognostic factor when N classification was based on site (TNM 1987) but not when based on number of positive nodes (TNM 1997) [57].

In particular, as regards SRC histology, the prognostic significance seems to be strictly "dependent on stage" according to a recent American study [58]. Indeed SRC adenocarcinomas show a more aggressive behaviour and lower disease-related survival compared to non-SRC tumours only in advanced stages. It has been hypothesized that "driver mutations controlling the metastatic potential of SRC may occur late in the course of disease, rendering SRC tumours which are relatively indolent in the early stages, highly aggressive in more advanced stages" [58].

The low survival rate reported for this subtype of gastric cancer in advanced stages is mainly related to the high potential of peritoneal dissemination when tumours involve serosa layer. Indeed as shown in Table 7.2, the largest survival gap between Eastern and high-volume Western series emerges for serosa arising tumours probably due to the higher percentage of diffuse-SRC type.

Thus, the prevalence of more aggressive cancers could explain the worse Western survival in advanced stages. Unfortunately, only few studies comparing Eastern and Western series according to gastric cancer subtypes are available yet. However, recent reports [59] suggested that when gastric cancer series with homogeneous clinico-pathological features are compared, survival between Eastern and Western patients is more similar than previously believed.

Disparities in tumour biology and patients' ethnicity may be additional factors responsible of different prognoses observed across the world regions.

Several recent studies reported a better outcome in Asian Americans than in other ethnicities, and these differences persisted when results were adjusted for several tumour or treatment-related factors [60, 61].

A recent Italian study documented different prognoses in patients with gastric cancer coming from different risk areas of Italy treated at the same centre with a similar surgical approach and staged in the same way [62]. Patients coming from Southern Italy, where the incidence of gastric cancer is very low, showed a worse outcome when compared with patients coming from Tuscany, a high-risk area. These results were confirmed even considering surgical and pathological factors previously included in an Italian prognostic score, thus suggesting biological differences between the groups [63].

Some studies have been conducted to investigate potential biological differences between Eastern and Western patients with gastric cancer, but these are limited to only a few cases or have reported conflicting results [64].

Unfortunately, reliable biological markers of gastric cancer aggressiveness are still unavailable, and patient-, tumour- and treatment-related differences between different series make this research subjected to inevitable bias.

Current Western Perspective

Considering the epidemiological aspects, management of gastric cancer in Western countries is currently focused on treatment of advanced, aggressive forms. In this context, multimodal therapies and tailored surgical approaches play a key role.

Multimodal Treatments

With the aims to increase the number of radical resections and to improve survival of gastric cancer patients, multimodal protocols have been evaluated.

Perioperative chemotherapy is the recommended multimodal treatment for locally advanced gastric cancer patients in Europe. Indeed two European randomized trials, the UK Medical Research Council MAGIC trial and the French FNCLCC/FFCD trial [65, 66], showed significant survival benefit in patients treated with perioperative chemotherapy compared with surgery alone. Of note, in these two trials, an elevated number of oesophago-gastric junction (EGJ) or lower oesophagus adenocarcinomas were enrolled (26% in the MAGIC trial and 75% in the FFCD trial).

However, EGJ adenocarcinomas are reported to respond better than gastric cancers to perioperative chemotherapy and the survival benefit, which is clear for EGJ tumours, seems questionable for gastric cancers [67, 68].

A GIRCG phase II study on perioperative chemotherapy is currently ongoing with the aim to specifically evaluate this multimodal approach in non-cardia gastric cancer (ClinicalTrials.gov Identifier: NCT01876927).

The lack of clear benefits from perioperative chemotherapy when considering only non-cardia gastric cancer may be due to different response of various subtypes. In particular, SRC tumours show a lower response rate compared to intestinal tumours, and this is associated to a worse prognosis [69].

Unfortunately, no results of randomized trials of perioperative chemotherapy stratified on tumour histotype are yet available. There is an urgent need to assess chemosensitivity in gastric cancer according to tumour subtype. Also, further studies on oncogenic pathways of SRC tumours and the identification of molecular targets for biological therapies are awaited.

Tailored Surgery

Gastrectomy with adequate resection margins and D2 lymphadenectomy is the standard of surgical treatment in Western high-volume centres. As previously reported, in Western countries tumours with aggressive behaviour are emerging; in this context extending surgery beyond D2 dissection could become a further therapeutic option.

Para-aortic nodes (PAN) are considered the last barrier between lymphatic vessels draining the primary tumour and the bloodstream. For this reason, they have been classified as distant metastases by TNM 1997 of the International Union Against Cancer. Nevertheless, even when metastases to PAN are documented, survival is not negligible, ranging between 17 [70] and 18% [37] after 5 years of follow-up.

The debate on super-extended lymphadenectomy has apparently come to an end after the publication of the Japan Clinical Oncology Group (JCOG) trial, which found no survival advantage in T2b, T3 and T4 gastric cancer when D2 lymphadenectomy was extended to PAN [37]. As a consequence, prophylactic D2 plus PAN dissection is no longer recommended as a first choice treatment in patients with curable gastric cancer by Japanese guidelines [71].

However, it should be reminded that in the latter trial the prevalence of No.16 metastases was rather low (8.5%) probably because only patients without macroscopic metastases to PAN were enrolled. Moreover, the JCOG trial, although not finding any significant survival advantage after PAN dissection with respect to simple D2 in the whole sample, highlighted significant interactions between T or N status and extension of lymphadenectomy ($p=0.004$ and $p=0.003$, respectively): patients with less advanced cancer (T2b and N0) showed a significant benefit from PAN dissection [37]. Indeed the authors tested 11 interactions, which moreover did not represent the primary end point of the trial. In our

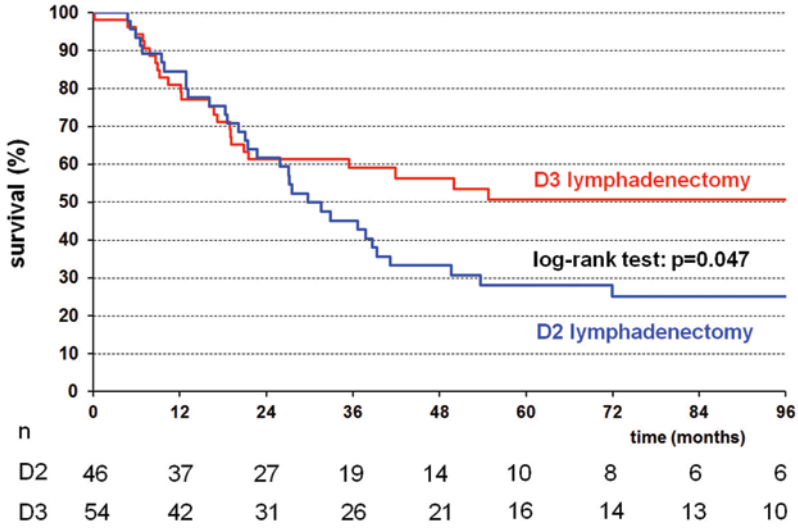

Fig. 7.3 Disease-related, Survival curves, estimated by the Kaplan–Meier method, after D2 and D3 lymphadenectomy in pT4a tumours with diffuse histotype arising from the body/antrum. The difference in survival was significant ($p=0.047$)

opinion, these interactions cannot be dismissed as multiple testing biases, not only because they are highly significant but also because they involve the most important prognostic variables in a consistent way.

In a GIRCG series of 598 patients, we highlighted a significant benefit after the super-extended procedure in T4a tumours with diffuse histotype arising from the body/antrum (partly unpublished GIRCG series) (Fig. 7.3) [72].

Thus, D2 lymphadenectomy is the standard procedure for advanced gastric cancer but D3 lymphadenectomy, whose benefit has not been proved by the JCOG trial [37], could nonetheless be useful in a subgroup of advanced gastric cancer patients.

In a recent study from the Stomach Cancer Study Group of the Japan Clinical Oncology Group [73], patients with locally advanced gastric cancer with extensive regional and/or PAN metastases were treated with neoadjuvant chemotherapy (S-1 plus cisplatin) followed by extended surgery with PAN dissection. Late results were satisfactory (3- and 5-year overall survival rates of 59 and 53 %, respectively), so the authors concluded that further investigation of this treatment strategy is warranted.

In the era of tailored treatment, the extension of lymphadenectomy cannot be the same in all patients with gastric cancer [74], but it should rather be tailored to the characteristics of cancer.

Conclusions

There is a wide geographical variation in gastric cancer incidence with remarkable differences between Eastern and Western countries. Over the last 30 years, there has been a marked decline in age-standardized incidence of gastric cancer worldwide mostly attributed to a fall in incidence of distal, intestinal type tumours, which correlates with the decreasing prevalence of *H. pylori* infection [4].

A higher proportion of cardia, proximal and diffuse-type gastric cancer, especially SCR, is currently reported in countries with lower incidence and mortality rates of stomach cancer.

It has been demonstrated that, when performed by experienced surgeons, D2 lymphadenectomy is a safe and adequate treatment also for Western patients.

Although specialized high-volume Western centres currently provide high-quality

standardized surgical management of gastric cancer patients, survival rates are still lower than those reported in Eastern series. The largest survival gap is observed in advanced stages that accounts for the majority of tumours in Western world. The higher proportion of more aggressive gastric cancer subtypes could explain the worse prognosis in Western countries.

Due to significant epidemiological and clinical differences between the East and the West, there is a substantial divergence in the current perspective on gastric cancer. Indeed while Eastern surgeons are focused on prevention, early detection and mini-invasive treatment of gastric cancer, in the Western world extended tailored surgery and multimodal approach remain the main therapeutic options.

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Part II

Diagnostic Techniques for Gastric Cancer

Diagnosis, Staging, and Workup of Gastric Cancer

8

Arvind Sabesan and Joseph J. Bennett

Abbreviations

AJCC	American joint committee on cancer
EUS	Endoscopic ultrasound
NCCN	National comprehensive cancer network
PET	Positron emission tomography
GEJ	Gastroesophageal junction
UICC	Union for international cancer control

Introduction

Gastric cancer remains a significant health issue and accounts for the 4th leading cause of cancer and the 2nd most common cause of cancer death worldwide [1, 2]. Although the incidence of the disease is declining, there have not been any improvements in earlier detection. The symptoms of the disease are vague and tend to overlap with other common and benign conditions [3]. In addition, many patients may prolong seeking medical care until symptoms become severe. Unfortunately, many patients already have advanced incurable disease at the time of presentation. Since patient symptomology is nonspecific, diagnosis of gastric cancer mainly relies on a heightened suspicion of the clinician along with multiple diagnostic modalities that ultimately end in tissue diagnosis [4]. Over the past few years there have been improvements in endoscopy, ultrasound, and imaging which now allow one to make the diagnosis of gastric cancer as well as gather other important prognostic indicators.

Although surgery remains the mainstay of treatment; trials have shown improved survival with the addition of chemotherapy and radiation [5–7]. With multiple options for treatment, algorithms have become more complex in regards to the sequencing and timing of the different multimodality treatments. This places an increased importance on accurate clinical staging in order to determine the best treatment plan. With the recent 7th edition of the American Joint Committee on Cancer (AJCC) staging manual, more emphasis is now placed on level of nodal involvement and staging groups have changed from prior versions [8]. This has important implications for patients in terms of overall survival and treatment offered. In addition, the nomogram model may provide more accurate prognostic information based on various patient and tumor characteristics, above and beyond the AJCC staging. Advances in molecular and genetic testing may also identify disease at a point well before a patient becomes clinically symptomatic or before radiographic disease is detected, with a further goal of identifying patients at risk of developing cancer

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before carcinogenesis is fully established. Staging systems of the future will hopefully be more individualized as compared to the cookie-cutter staging the AJCC currently uses. The ultimate goal with any cancer therapy should be improved survival and quality of life for the patient. Therefore, the workup of gastric cancer after tissue diagnosis should be focused on quickly identifying patients who are candidates for surgical resection versus those who many benefit from neoadjuvant chemotherapy. In addition, patients who present with metastatic disease should be offered palliative chemotherapy or surgery for patients with symptoms of bleeding or obstruction. The myriad of tools available to workup patients with gastric cancer such as high resolution CT scan, MRI, diagnostic laparoscopy, endoscopic ultrasound, and positron emission tomography (PET) scan should be utilized in an efficient and coordinated manner. Endoscopy should always be at the top of the list when a diagnosis of gastric cancer is being entertained. Direct visualization and tissue biopsy ultimately need to be performed, and information gained from endoscopy may direct all further testing necessary. For vague symptoms such as abdominal pain, bloating or reflux, cross-sectional imaging is often done first, initiating the gastric cancer evaluation. High resolution CT is a very accurate modality to assess for systemic disease, evaluate for nodal metastases, as well as provide the surgeon anatomical information about the primary tumor, surrounding vessels, and nearby organs [9]. Diagnostic laparoscopy should be used selectively to identify radiographically occult malignant disease or contraindications to surgical resection, potentially sparing the asymptomatic patient from an unnecessary laparotomy. The workup of a patient with newly diagnosed gastric cancer should use select tests in order to provide the optimal treatment with minimal delay and morbidity to the patient.

Diagnosis

Gastric cancer is usually asymptomatic until it progresses to an advanced stage. Many of the early symptoms of gastric cancer are also common to other diagnoses such as dyspepsia or ulcer disease [10]. These symptoms are often thought to be gas, reflux, biliary colic, irritable bowel, and are then treated with antiulcer therapy which may mask symptoms or delay ultimate diagnosis [4]. Certain alarm features should heighten clinical suspicion and should prompt earlier use of upper GI endoscopy. These symptoms include anorexia, unintentional weight loss, dysphagia, recurrent vomiting, or early satiety. In a study of 1121 patients at Memorial Sloan-Kettering Cancer Center, the most common presenting symptoms were anorexia, weight loss, pain, and vomiting [11]. The pain associated with gastric cancer tends to be mild and localized to the epigastric region and can mimic ulcer disease and may even be relieved by eating. As the disease progresses the pain may become more severe in duration and nature. Certain complaints may provide clues to the location of the primary tumor. Cardia or gastroesophageal junction (GEJ) tumors may present with dysphagia while antral tumors may present with signs of gastric outlet obstruction. Complaints of early satiety may be related to a type of diffuse gastric cancer called linitis plastica which prevents distention of the stomach. Rarely, tumor invasion into the transverse colon many even present as colonic obstruction.

The majority of patients will not have significant physical exam findings and the presence of findings is usually due to metastatic disease. Palpable supraclavicular nodes (Virchow) or periumbilical nodes (Sister Mary Joseph), or the presence of abdominal ascites and resulting distention are all poor prognostic signs. Few patients will also present with a bowel obstruction from carcinomatosis. In addition, a rectal mass (Blumers shelf) may indicate drop metastasis into the pelvis [10]. Occult bleeding from the tumor may present as Guaiac positive stool, however gross upper or lower gastrointestinal bleeding is rare. Iron deficiency anemia is not an uncommon presentation, as many of these tumors are friable enough to cause a chronic anemia but without signs or symptoms of an acute hemorrhage. Such patients may present with very low hemoglobin levels, fatigue, shortness of breath, syncope, or mild tachycardia, and orthostatic hypotension.

Diagnostic Modalities

Since physical exam findings are usually a marker of metastatic disease, diagnostic tests such as a barium swallow or an upper endoscopy are the mainstay for diagnosis of curable gastric cancer. These studies should be considered right away when gastric cancer is being considered in order to prevent a delay in diagnosis and treatment. Persistent or refractory upper GI symptoms are indications to pursue imaging and endoscopy, as described below. Barium studies, while used frequently in the past, now play less of a role in the workup of gastric cancer and upper GI symptoms, in general. Characteristics such as an intraluminal mass, irregular rugae, and thickening of the gastric wall were signs of underlying malignancy. The drawback of barium studies is the sensitivity, which can be as low at 14% in the detection of malignancy [12]. One instance in which barium study can be advantageous over endoscopy is in the diagnosis of linitis plastica. The study will show the characteristic "leather-flask" and nondistensible appearance of the stomach while endoscopic view may be normal appearing.

The American Gastroenterological Association recommends an endoscopy in patients over the age of 55 who present with new onset dyspepsia [9]. Worrisome findings such as weight loss, vomiting, should prompt early endoscopy as well. In addition, endoscopy should be strongly recommended for high risk patients such as Asians, Native Americans, patients who exhibit persistent symptoms despite antiulcer therapy, absence of NSAID use, and patients with a family history of gastric cancer. These populations have a high risk for malignancy and careful endoscopy should be carried out. Endoscopy provides direct visualization of the upper GI tract and allows for identification and biopsy of masses or ulcers (Fig. 8.1). The use of endoscopy has a 90–96% accuracy in the diagnosis and detection of gastric cancer [13].

In early gastric cancer, abnormalities can presents as superficial plaques or depressions, polyploidy protrusions, or mucosal ulcerations. Advanced gastric cancer will usually present as a large space occupying mass, deep ulcerated lesion, or areas of abnormal infiltration and thickening. The advantage of endoscopy over other diagnostic modalities is that any abnormal area

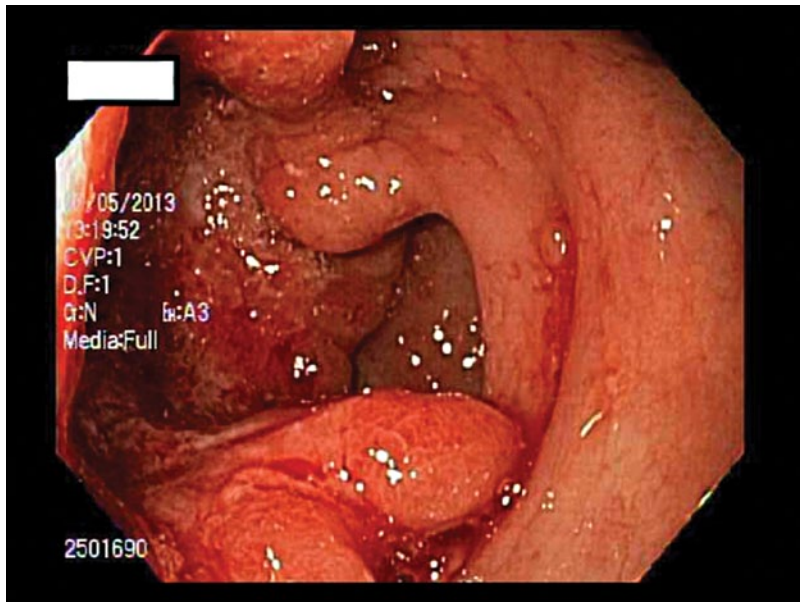

Fig. 8.1 Large ulcerated and bleeding adenocarcinoma in the antrum in a patient who presented with anemia

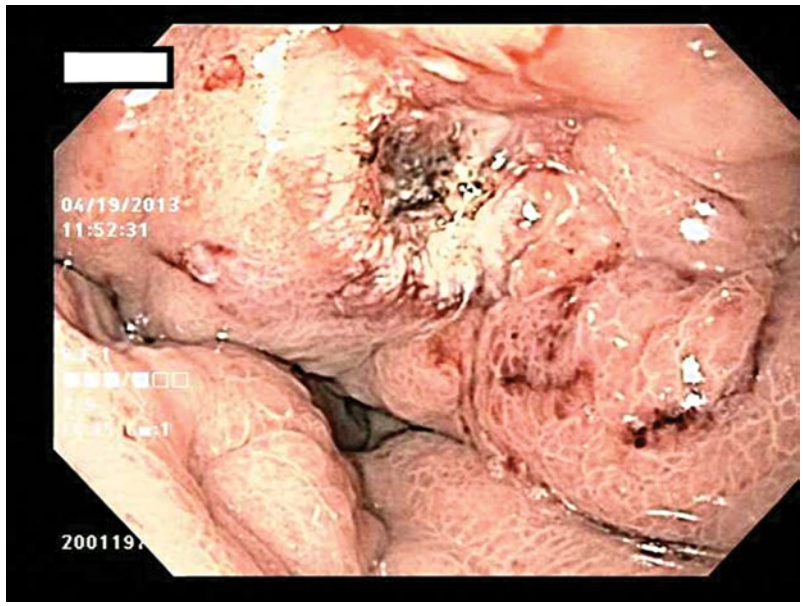

Fig. 8.2 Ulcer in the gastric cardia which was biopsy proven adenocarcinoma

can be easily biopsied. Although it may seem obvious, the difference between benign and malignant gastric ulcers may be difficult to differentiate based on appearance alone. As a general rule, benign ulcers tend to assume regular shapes such as round or oval and have a smooth even base. The border between the ulcer and the surrounding mucosa tend to be sharply demarcated. Conversely, malignant lesions tend to have irregular shapes, possibly necrotic bases and irregular borders. Biopsy is used to establish malignancy in an ulcer and six to eight biopsies from the edge and base of the ulcer are recommended (Fig. 8.2). This will provide a 98% sensitivity of malignancy detection. A suspicious lesion may even warrant repeat sampling at the same site in order to obtain deeper tissue, which may be harboring malignancy. This is especially important in cases of diffuse type gastric cancer (linitis plastica). These tumors tend to infiltrate the submucosa and muscularis propria and superficial biopsies may be negative. In addition, it is important to perform random biopsies beyond the lesion in question in order to increase diagnostic yield [13] (Fig. 8.3). The updated Sydney system recommends two biopsies from the corpus, two from the antrum, and one from the angularis insicura [10]. Along with biopsies, brush cytology has been used; however with adequate number of biopsy samples, this may not be needed.

Endoscopic Enhancement

Although the diagnosis of gastric cancer has been mainly achieved with standard white light endoscopy, new technologies have emerged which can now identify smaller lesions as well as provide fine endoscopic detail of the mucosa. This is especially important with the increased use of endoscopic mucosal resection. In many instances, small lesions, which may present as a flat or superficial depression, are difficult to separate from benign disease. New technologies such as magnification endoscopy, endocytoscopy, narrow band imaging, and confocal laser endomicroscopy, allow high-resolution evaluation of a suspicious area. These modalities are combined with topical stains such as acetic acid and indigo carmine which allow the endoscopist to distinguish between benign and malignant lesions. These lesions are identified by evaluating the mucosa for abnormal changes such as lack of subepithelial capillary network pattern or irregular

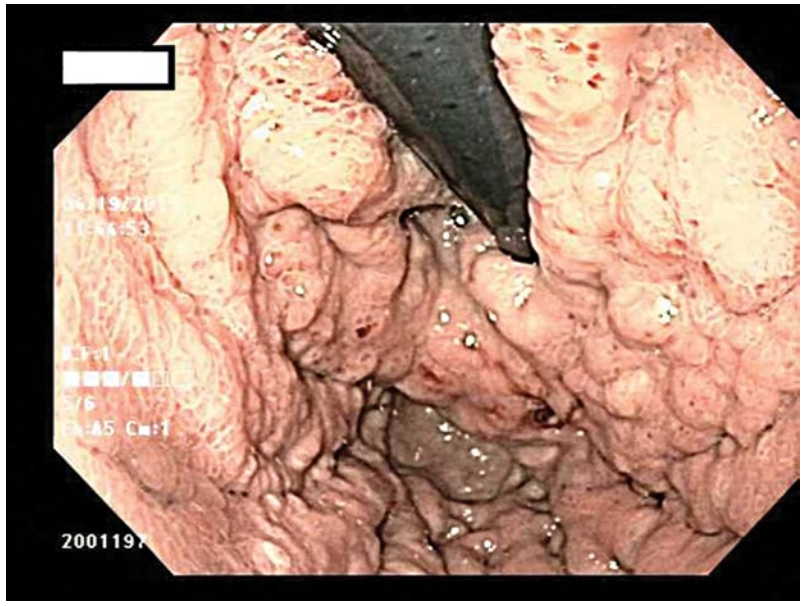

Fig. 8.3 Patient who presented with anemia and was found to have a gastric ulcer. The stomach showed poor distensibility on endoscopy and biopsies were positive for linitis plastica

microvasculature. Studies have also shown that with staining, carcinomas tend to return to their baseline color much faster than benign lesions [13]. In a study of 136 patients, Dinis-Ribeiro et al. were able to achieve a sensitivity and specificity of 76% and 87% for identifying intestinal metaplasia and 98% and 81% respectively for dysplasia [14]. Although these technologies have not been implemented as standard of care, they are able to identify abnormal lesions which may not have been picked up with standard white light endoscopy. As these technologies evolve, smaller lesions may be able to be picked up at an earlier stage and facilitate endoscopic mucosal resection or earlier gastrectomy with better patient outcomes.

Screening Programs

Since gastric cancer tends to present at a later stage, many countries with a high incidence of the disease have instituted screening programs. Japan uses a program where patients over the age of 40 have a double contrast barium study with a subsequent endoscopy if any abnormality is detected. In addition, serum pepsinogen tests are used to screen for patients who have risk for atrophic gastritis. Since the institution of this screening system, there has been a reduction in gastric cancer specific mortality as well as an increased 5-year survival for patients who undergo screening. Although this screening method has been validated, it is only practical and cost effective in countries with a high incidence of gastric cancer. In the USA where the gastric cancer rate is about 8x less common than Eastern Asian countries, the cost of a similar screening program is projected to be ten times more expensive with potentially no benefit. In theory, a more practical solution is to assess for the presence of risk factors and to screen those patients selectively. These would include patients with a history of previous gastrectomy, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer or strong family history of gastric cancer. The optimal timing and subsequent interval for serial endoscopies in these high risk patients is unknown, and there is no clear evidence that screening improves survival. In most instances, follow up screening is left to the discretion of the physician based on patient history, risk factors, and findings on the

initial endoscopy. Currently, mass screening does not seem practical in countries where the incidence of the disease is low [13].

Tumor Markers

Many tumor markers have been shown to have an association with gastric cancer. These include markers such as CEA, CA 19−9, and CA 72−4. However, the usefulness of these markers is up to debate with reports of varying sensitivity and specificity in the detection of disease based on tumor burden. Of the markers available, CEA and CA 19−9 appear to be the most useful [15, 16]. In one study performed by Nakane et al., CEA level was elevated in 249 out 865 patients with gastric cancer [3]. They were able to find a correlation with stage as well as survival. Patients who had a CEA level less than 10 ng/ml were found to have longer survival. In addition, some smaller studies have suggested a prognostic role for preoperative CA 72−4 levels. Despite these findings however, tumor markers have not been widely used for screening, prognosis, or for long-term follow up. The sensitivity and specificity of these markers is low and preclude any significant clinical use. A rise in tumor levels may indicate worsening disease or recurrence. Likewise, a drop in levels post treatment may indicate a response; however clinical decisions are never based upon tumor markers alone. The NCCN (National Comprehensive Cancer Network) guidelines do not include tumor markers in the workup, staging or follow-up in patients with gastric cancer.

Staging

Cancer staging is a crucial component in providing optimal treatment for patients with any malignancy. Although the components of staging may vary depending on the type of cancer, the overall goals of staging the patient remain constant. From the view of the clinician, staging identifies the most important prognostic factors for that particular tumor such as depth of invasion, tumor size, lymph node status, and the presence or absence of metastatic disease, all of which ultimately affect survival. Once the clinical staging is complete, patients are now stratified according to disease severity, and stage is able to direct the best course and order of treatment. Depending on stage, goals of treatment are defined and the patient is directed toward long-term cure, treatment to prolong quantity and quality of life but without cure, or offering palliative treatment only. Although staging is ultimately divided into four categories with several subcategories, from a practical perspective, patients are first determined to have metastatic disease or not, and are then assessed to have resectable disease or not. For patients with resectable disease, clinical staging is helpful in determining if patients are best treated with surgery first or neoadjuvant therapy, and then after surgery, when pathological staging is available, if adjuvant treatment is necessary. Certainly these decisions are best made in the multidisciplinary setting among surgeons, medical oncologist and sometimes, radiation oncologists.

Another benefit of staging is the ability to generally predict patient survival. This is important when toxic treatments such as chemotherapy or radiation need to be justified to the patient, and also to explain the patients why curative surgery is or is not an option, as most patients know that removing a solid organ cancer is the only option for cure or for long-term survival. Staging is also extremely important when entering patients into clinical trials. Most new treatments are studied within the setting of metastatic disease, so properly diagnosing stage IV disease may enable a patient to get otherwise unavailable and novel therapies. For patients in adjuvant or neoadjuvant trials, proper staging is paramount to avoid stage migration and unnecessary biases within the trial, resulting in un-interpretable data. Finally, staging provides population based statistics for different cancers, and allows outcome data for different treatment modalities to be compared on a large-scale basis. Such information may be necessary to make public health decisions, such as for screening programs or for funding for various local, state or federal programs.

Table 8.1 7th edition AJCC TNM staging system—anatomic stage of Gastric cancer

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0 or N1	M0
	T4a	N2	M0
	T3	N2	M0
Stage IIIC	T4b	N2 or N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

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The staging system for gastric cancer has undergone numerous revisions. The main tumor staging system is the AJCC/UICC TNM classification which evaluates the depth of the primary tumor, lymph node involvement, and presence of metastatic disease (Table 8.1). Development of an effective gastric cancer staging system has been particularly difficult for many reasons. First, accumulating evidence has shown a difference in survival based on the anatomic location of tumors within the stomach. Proximal and GEJ tumors have been shown to have a worse prognosis than distal tumors. Many times these GEJ tumors are bulky and the exact origin of these tumors cannot be determined. This creates a problem of staging the malignancy as esophageal or gastric. For this reason, GEJ cancers have been further stratified by the Siewert classification, as described below. The 7th edition of the AJCC staging also places more emphasis on lymph node involvement, which has been shown to be a major determinant in survival for gastric cancer. The number of positive lymph nodes needed to N-stage patients has changed dramatically from one edition to the next. The pendulum has swung from needing only one or two positive lymph nodes to go from one N-stage to another several editions ago, to needing many nodes for each N-category, and now back to only a few nodes in each N-stage once again in the 7th edition. These changes are all meant to more accurately stratify patient survival. Finally, there has been improved recognition that positive peritoneal cytology has a similar prognosis as distant metastatic disease and this has been appropriately reflected in the current staging system as well [8].

GEJ Tumors

One of the major changes in the 7th edition of AJCC gastric cancer staging is the management of GEJ tumors. In the past, there was ambiguity of the origin of the tumor and they could be staged as esophageal or gastric depending on the physician. After analysis of a large data set assembled by the Worldwide Esophageal Cancer Collaboration a consensus was developed to use the Esophageal cancer staging system for GEJ tumors. More specifically, any tumor arising in the GEJ or tumors that arise within 5 cm of the GEJ, and cross the GEJ are now staged as esophageal cancers. Tumors that originate in the proximal 5 cm of the stomach, but do not cross the GEJ are staged with the revised gastric cancer system. This reflects the difference in behavior of proximal versus distal gastric tumors [8].

T Staging

The revised T staging is shown in Table 8.2. The T staging is based upon the depth of invasion of the primary tumor. Important changes include the standardization of the T staging throughout the gastrointestinal system. Compared to the 6th edition, now T1 category has been split into T1a and T1b. T1a denotes tumors that invade up to the muscularis mucosa and T1b denotes tumors that invade up the submucosa. This distinction

Table 8.2 7th edition AJCC tumor staging designation—T category definitions for Gastric cancer

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4a	Tumor invades serosa
T4b	Tumor invades adjacent structures

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is very important because gastric cancer, unlike other malignancies, has a propensity for lymph node metastasis even when confined to the lamina propria, so the distinction between Tis, T1a, and T1b is important and necessitates a subcategory. This is in contrast to the 6th edition in which the T2 stage was subdivided into T2a and T2b, which denoted invasion of the muscularis propria and subserosa respectively. Now tumors which invade the subserosa are classified at T3, which reflects the worse prognosis of these deeper invading tumors. Upstaging from T2 to T3 now puts each tumor in a higher grouping for all stages [17]. Another important fact to note is T3 also includes tumors that invade into the gastrocolic or gastrohepatic ligaments without perforation of the visceral peritoneum covering these surfaces.

Management of tumors which penetrate the serosa has also undergone change. Previously these were classified as T3 but with the 7th edition they have been upstaged to T4a. This reflects the understanding that serosal involvement is a negative prognostic factor and denotes a higher stage. T4b now denotes tumors which have invasion into local structures. Under the new staging, a patient could have a T4b tumor along with positive nodes and still be classified as a stage 3, showing that en bloc surgical resection of involved organs with lymph node dissection is still a strategy for curative intent and these patients have different survival compared to truly metastatic disease. Overall the T staging of the 7th edition provides synchrony among all tumors of the GI tract and reflects a better understanding of overall survival based on depth on invasion

N Category

The N category is based on the number of positive regional lymph nodes. It is still classified at N1, N2, and N3 and is unchanged from the 6th edition. However, the number of positive lymph nodes required for each category has changed significantly (Table 8.3). Current N1 now reflects 1 to 2 regional nodes, where previously up to 6 positive nodes could be considered N1. Current N2 reflects up to 6 positive nodes where previously up to 15 nodes could be considered N2. N3 now requires 7 or more nodes where

Table 8.3 AJCC 7th edition Nodal designation—N category definitions for Gastric cancer

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 2 regional lymph nodes
N2	Metastasis in 3 to 6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

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previously greater than 15 nodes were required. Essentially, fewer nodes are now required to increase the N stage. This change is based on the understanding that nodal involvement changes survival significantly and is an important prognostic factor. Even involvement of one node changes a patient's stage and negatively affects survival. One important distinction between the 6th and 7th edition is the category of N3. In the previous staging, N3 would designate a patient as stage IV. In the new staging a patient can have N3 designation and could be stage II or stage III. This reflects a change, and even though high nodal disease is a poor prognostic sign it does not designate someone as having stage IV metastatic disease. Another problem with the 6th edition staging was the problem of stage migration. If a patient had an inadequate lymph node dissection with minimal nodes harvested, they would be understaged. With the requirement of less positive lymph nodes in the 7th edition, this reduces the effect of stage migration, as long as the total number of retrieved nodes is more than seven [8, 17]. Unfortunately, such changes may have been necessitated to make up for operative staging inadequacies if surgeons are not properly performing a good lymph node dissection and harvesting the still recommended 15+nodes. Overall, the changes in the nodal category reflect the understanding that lymph node involvement is a poor prognostic sign and significantly upstages a patient. In addition, it attempts to reduce stage migration by requiring less nodes for each respective N category which may prevent patients from being understaged. This staging change should not take the burden off the surgeon to perform a proper operation, however.

Stage IV Disease

One of the biggest changes of the 7th edition AJCC staging is the division of the 6th edition stage IV category into multiple stage II and III categories. Previously, a patient could be categorized as stage IV metastatic if they had distant organ involvement or stage IV nodal if they had a large burden of positive lymph nodes. It is now known that gastric cancer without distant metastasis has a better prognosis, so stage IV nodal category has been removed and redistributed in the earlier stages reflecting the improved survival [17].

Another major change from the 6th edition is the M1 designation. The 6th edition required distant organ involvement for M1 classification. Long-term survival data showed that patients with positive peritoneal cytology as having extremely poor prognosis, and have survival which is similar to patients with distant metastatic disease. Therefore, positive peritoneal cytology is now classified as M1 disease with similar prognosis as patients with distant organ involvement [17] .

Nomogram Staging

AJCC staging is helpful but it places patients into broader categories and does not necessarily reflect what will happen to an individual person. Other variables such as age, gender, tumor size, and location also need to be considered. The AJCC staging also does not place different weights to these variables, which the nomogram attempts to do. In a study of 1136 patients at MSKCC who had an R0 gastrectomy, a nomogram was created to estimate the 5-year cancer specific survival [18]. By incorporating multiple patient and tumor characteristics the nomogram was found to have a better predictive ability for survival when compared to the AJCC staging system. The nomogram calculates survival for each individual person rather than broadly grouping patients into a few stages and then assigning a survival percentage to that group. Nomogram results may be used to more accurately determine adjuvant or experimental treatment verses the AJCC staging.

Molecular Classification and Targeted Therapy

The current staging of gastric cancer incorporates tumor depth, lymph node status, and the presence

of metastatic. Although these variables are important, there are many other factors such as anatomic location and histopathologic features that are known to influence cancer behavior as well as response to treatment. For example, GEJ tumors are known to behave and present differently when compared to distal or diffuse type tumors. The Lauren classification subdivides gastric cancer into intestinal, diffuse or mixed subtypes, each of which are known to have different clinical behavior. Despite these recognized differences, the treatment of gastric cancer is not varied based upon anatomic or histopathologic differences. In addition, adjuvant treatment is broadly applied to all disease subtypes. This is in contrast to the treatment of other malignancies such as breast cancer where targeted therapy against molecular subtypes has shown improved survival. Similarly, gastric cancer may be better characterized by molecular and gene expression analysis which would allow more targeted therapy.

In a study by Shah et al., authors hypothesized that distinct gastric cancer subtypes (proximal, diffuse, distal), could also be identified based upon gene expression analysis [19]. They examined 57 patients and used a genomic classifier to identify the gene expression of various gastric cancer subtypes. The study was able to show that gastric cancer subtypes based on anatomic location or histopathologic features indeed have unique genes that distinguish them from normal gastric tissue as well as distinct gene expression that can separate the various types of gastric cancer. There was an 85% ability to distinguish gastric cancer subtypes by gene expression. This provides evidence that gastric cancer subtypes may be distinguished molecularly.

Molecular targets are currently being used in gastric cancer. One currently defined biomarker in gastric cancer is human epidermal growth factor receptor (Her-2-neu), which is overexpressed in about 25% of patients. Patients who express this marker have improved survival when treated with chemotherapy regimens, which include trastuzumab (anti-Her2 antibody) [20]. Thus as molecular classification of tumors improves, more targeted therapy may be developed, which may provide better treatment options for patients. Although Her2 status is not included in gastric cancer staging currently, in future editions it may be incorporated. This may be especially useful in nomogram types assessments where multiple variables are used to prognosticate patients.

Workup

Goals of the Workup Process

The purpose of the workup process is to collect information which will ultimately guide treatment recommendations. Once this process is complete, patients should be stratified into one of two immediate groups. The first group consists of patients who will be considered for resection and treatment with curative intent. The second group consists of patients who have unresectable disease and need to be offered palliative therapy, albeit with a multidisciplinary approach which still may include surgery. The combination of laboratory tests, imaging, and even invasive procedures should be coordinated in an organized and nonredundant manner to provide optimal treatment for the patient.

Consensus guidelines are provided by the NCCN for evaluation and workup of patients with gastric cancer [21]. Initially all patients with gastric cancer should have a complete physical exam and laboratory workup (Fig. 8.4). The workup should include a full chemistry panel, hepatic function tests, and complete blood count. In addition, a nutritional assessment of the patient should be completed. This includes markers such as albumin and prealbumin, but also assessment of the patient's weight and quantity of food intake as this may influence future surgical treatment. The preoperative evaluation should also include a CT of the chest, abdomen, and pelvis to evaluate for metastatic disease. Once this is complete, patients should undergo endoscopy with biopsy of the suspected lesion or mass. The technique of biopsy has been described previously. This not only provides tissue diagnosis, but allows assessment of the location of the lesion and the rest of

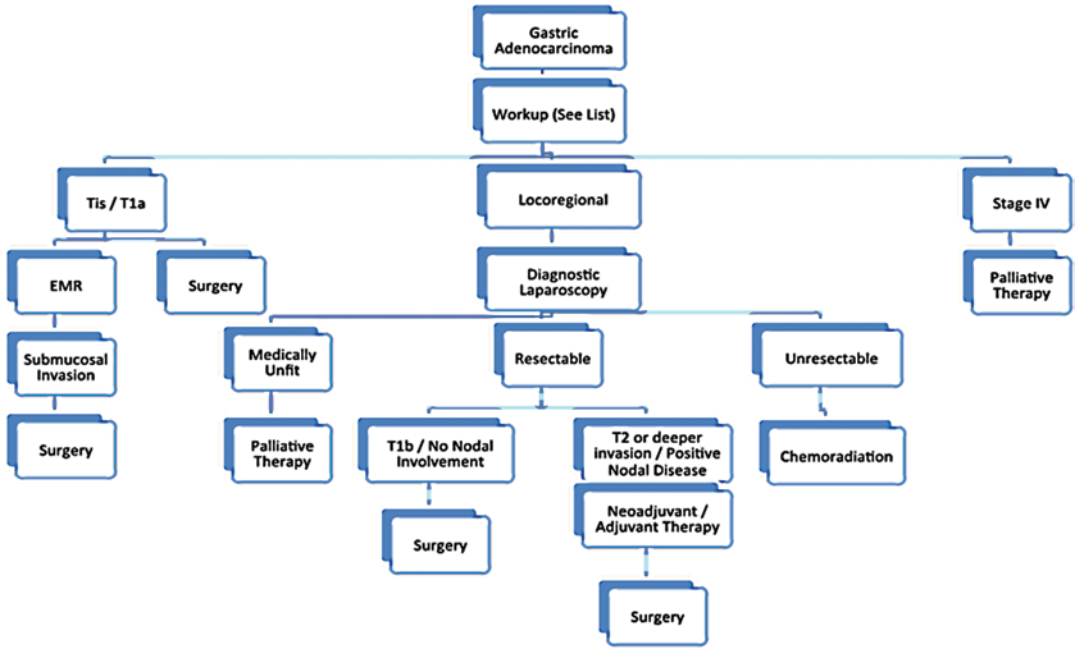

Fig. 8.4 Diagnostic algorithm for patients with gastric adenocarcinoma

the stomach. At this time endoscopic ultrasound may be performed if there is no evidence of metastatic disease. Additional tests and procedures such as PET scan or staging laparoscopy may be added in certain clinical situations.

After the completion of this initial workup, patients can now be stratified into two clinical stage groups. The first group consists of patients with locoregional disease who would be under the AJCC stage I–III, and the second are those with stage IV systemic disease. Stage IV patients are referred for palliative measures. A further treatment subdivision occurs in patients with locoregional Stage I–III disease, with patients who have early gastric cancer amenable to endoscopic mucosal resection, and patients who will require gastrectomy. Patients with early gastric cancer (Tis or T1a) should be evaluated by an experienced interventional gastroenterologist for endoscopic mucosal resection. Oftentimes, endoscopic ultrasound (EUS) is needed first to determine if the lesion is indeed T1a or less. This EMR technique avoids the morbidity of a gastric resection with anastomosis. Since these patients are unlikely to have nodal metastases, EMR is appropriate for the earliest of gastric cancers. Unfortunately, this early stage is rarely seen in North America. Stage I–III patients who are technically resectable, but who are medically unfit to have an operation or who choose not to have surgery, can be referred for chemotherapy and/or radiation therapy with the understanding that this is not a curative approach. There are also patients who are not Stage IV, but who have locally advanced disease and are deemed upfront unresectable by the surgeon. The patient may be clinical Stage III, but due to vascular encasement or multiorgan involvement, the tumor cannot be removed or the surgeon opts for a neoadjuvant approach. The surgeon will need to communicate with the rest of the team whether or not they believe the tumor can be downstaged to a resectable status, and will need to stay part of the team and reassess for resection after the first several cycles of chemotherapy and radiation therapy.

The remaining patients are those who are medically fit, able to tolerate surgical resection, and who are technically resectable. Various modalities including CT scan, endoscopic ultrasound,

staging laparoscopy, and PET scan are used to determine resectability and are explained below. Patients who are thought to be resectable are then referred for multimodality therapy, which includes surgical resection and chemoradiation. The order of this therapy is dictated by evaluation by a multidisciplinary team. At this point, all patients have been assigned a clinical stage based upon best estimate of tumor depth and presence of nodal or metastatic disease. Further treatment is based on pathological assessment of the tumor and/or response to neoadjuvant therapy. Finally, all patients are evaluated on their functional status and other comorbid conditions, which may exclude or change their treatment options.

CT Scan

Computed tomography scan is completed early in the workup of a patient with gastric cancer. It is widely available and noninvasive and provides immediate evaluation for metastatic disease. CT is performed with IV and PO contrast, which provides good resolution as well as adequate distension of the stomach to allow for evaluation of abnormalities. CT can easily assess for the presence of abdominal ascites, hepatic lesions, or adnexal metastasis. It is also useful in assessing for local invasion of the tumor into other organs or major vessels and aids in operative planning. The presence of major vascular or organ involvement may change operative management. In addition CT is also able to assess for bulky lymphadenopathy around the stomach. The presence of lymph nodes in the aortocaval region, or infrapancreatic region, are nodes that are outside the field of surgical resection and would confer unresectability.

One drawback of CT scan is the fact that it does not allow for the assessment of metastasis that are smaller than 5 mm [9]. There could be peritoneal or liver disease under this size which would not be picked up on CT scan and would contraindicate surgical resection. In addition, 20–30% of patients may have intraperitoneal disease upon surgical exploration that was not found on CT scan. This information has to be conveyed to the patient before undergoing potential resection.

An important aspect of staging and treatment is assessment of the T stage of the primary tumor. According to the NCCN guidelines, tumors that involve the muscularis propria (T2) or deeper could receive neoadjuvant therapy to improve the likelihood of surgical resection. Previously, CT had been considered a poor modality for evaluation of the T stage with a wide accuracy rate of 43–82%. However, the CT scanners used in these studies were single detector and had cross sections of 5–10 mm. The speed of the scan was slow and motion artifact was common. With the advent of multidetector high resolution CT scanning, images now have better diagnostic performance. Bhandari et al. evaluated MDCT in comparison with EUS and found no major difference in diagnostic accuracy, sensitivity, or specificity in estimation of the T stage and presence of serosal involvement [22]. As technology improves, and with increased use of 3D reconstruction, CT may become an increasingly useful modality in evaluation of the T stage.

Endoscopic Ultrasound

The NCCN guidelines include the use of endoscopic ultrasound in the workup of patients with gastric cancer; however use varies based on institution. The two main uses of this modality are estimation of the T stage of the lesion as well as evaluation for positive nodal disease. An ultrasound probe at the end of the endoscope is used to differentiate the different layers of the gastric wall and can be used to estimate the depth of penetration of a tumor. Depending on the type of ultrasound, 5–9 layers of the gastric wall can be seen. High-resolution images are obtained at the expense of limited depth penetration. With the increased use of endoscopic mucosal resection and neoadjuvant therapy an accurate assessment of the T stage is necessary in order to properly guide management.

Many studies have been done that assess the ability of EUS to differentiate the layers of the gastric wall. A recent large meta-analysis that

evaluated 54 studies reported that EUS had a sensitivity and specificity of 86% and 91% respectively in distinguishing T1 to T2 versus T3 to T4 [23]. However, the ability of EUS to distinguish specific T stage was not as accurate. In addition, the studies that evaluated EUS were done based on the old TNM staging system. So when extrapolated to the current 7th edition staging, the strength of EUS is really differentiating T1 to T3 versus T4. When considering offering neoadjuvant therapy in which the distinction between T1 and T2 lesions is crucial, EUS may not be accurate in providing this information. The main drawback of EUS may be in the assessment of true T3 lesions due to potential under staging or over staging based on lesion characteristics [13].

When considering a patient for EMR, invasion of the muscularis propria (T2) needs to be excluded because it is a contraindication for this therapeutic modality. EUS may be a useful tool for this distinction and a recent large study found that EUS has a good sensitivity (83%) and specificity (96%) for distinguishing early cancer (T1) from advanced [13]. However, the ability to distinguish T1a from T1b lesions was more varied. With further study EUS may be a useful modality for assessment of EMR in select patients.

The other utility of EUS is in the evaluation of nodal disease. Unfortunately, EUS only has a sensitivity of 69% and specificity of 84% for assessment of lymph node involvement. One advantage of EUS is the ability to perform fine needle aspiration of suspicious nodes to evaluate for malignancy. Characteristics of involved nodes may include size greater than 1 cm, hypoechoic pattern, or sharp contour.

Although EUS is recommended by the NCCN guidelines, its application in the workup of gastric cancer needs to be carefully chosen. It can provide good estimation of T stage groups and has the ability to detect nodal involvement, which may lean the clinician toward neoadjuvant therapy or the use of staging laparoscopy before surgical resection. EUS does however have limitations and certain areas of the stomach such as the posterior fundus and lesser curvature may not be amenable to complete evaluation. EUS has also been used for evaluation for metastatic disease. The right lobe of the liver is amenable to ultrasound as well as fine needle aspiration. In addition, EUS has been found to be able to detect even trace amount of ascites. Although, this cannot replace staging laparoscopy, it may be useful in predicting peritoneal metastasis. In past studies EUS has been quoted as the superior modality in assessing the T stage, however with improvement in multidetector CT, similar accuracies have been found between the two. Depending on the patient and tumor characteristics, EUS may not be needed when high resolution imaging of the lesion is available via CT.

Staging Laparoscopy

Staging laparoscopy allows a detailed evaluation of the liver surface, peritoneum, stomach, regional lymph nodes as well as evaluation for abdominal ascites. This modality provides several benefits. One benefit is the ability to perform cytologic analysis of the peritoneal fluid, which has important implications. Patients who have positive cytology have poor prognosis and are at high risk of recurrence after surgery. In the 7th edition of the AJCC staging manual, positive peritoneal cytology is considered M1 disease, which would contraindicate surgical resection. In addition, these patients may have prolonged survival with chemotherapy, which should be offered to these patients instead of surgery.

Another benefit of laparoscopy is the ability to detect metastatic disease and to spare patients the morbidity of a nontherapeutic laparotomy. The preoperative staging of patients with gastric cancer includes endoscopy, EUS, CT and potentially PET scan. Even when staging with these modalities is negative, a large portion of patients will be found to have liver or peritoneal metastasis or nonregional lymph nodes upon surgical exploration. It is believed that up to 30% of patients will have evidence of metastatic disease when taken to the operating room despite a negative preoperative workup. In these patients, there have been no evidence of benefit of surgical resection, and palliative surgery for reasons

such as gastric outlet obstruction or bleeding is rarely needed. In addition, the insult of a nontherapeutic laparotomy prolongs hospital course, delays the start of chemotherapy, and may be associated with perioperative complications. In light of this fact, many have considered staging laparoscopy as a means to evaluate for metastatic disease before plans for definitive surgical resection. In a study at MSKCC, staging laparoscopy was evaluated in patients over the age of 65 who presented with gastric cancer [24]. Over an eight year period, 11759 patients were evaluated with gastric adenocarcinoma, and 6388 patients had an operative procedure. Staging laparoscopy was performed in 506 (7.9%) patients. 151(29.8%) of these patients evaluated by laparoscopy had unresectable or metastatic disease. The use of staging laparoscopy spared these patients a nontherapeutic laparotomy. In addition, when compared to patients who underwent noncurative laparotomy, there was a lower rate of in hospital mortality and shorter length of hospitalization. The findings show that a large portion of patients who appear resectable will be upstaged to metastatic disease and are not candidates for curative resection. Noncurative laparotomy with potential wound problems, postoperative ileus, and possible debilitation from a more prolonged hospital stay, all may contribute to a delay in starting chemotherapy in the very patient population that needs systemic treatment the most. Comparatively, laparoscopy is a short, out-patient surgery.

The NCCN guidelines recommend that patients suspected of having subserosal (T3) or nodal involvement, be evaluated for staging laparoscopy with peritoneal cytology. These guidelines come with a category 2B recommendation. This has the benefit of identifying metastatic disease in a large portion of patients without the use of laparotomy. Thus patients who appear resectable but have occult disease are spared the morbidity of a laparotomy. In addition, the diagnosis of metastatic disease is diagnosed in a minimally invasive way, which allows patients who would benefit from chemotherapy to begin treatment without significant delay.

PET/CT

PET scan is an increasingly used modality in the detection, staging and management of various malignancies. The NCCN guidelines do recommend the use of PET and PET/CT when clinically indicated, however specific clinical scenarios are not given. The use of PET imaging in gastric cancer is fraught with many issues. PET scan functions by detecting the level of radiolabeled glucose molecules in the body. Unfortunately, many gastric cancers such as mucinous and diffuse types are not PET avid. This lowers the sensitivity of PET for identification of disease. In addition, the poor spatial resolution of PET renders it a nonsensitive modality for evaluation of the T stage as well as nodal involvement. PET/CT has a sensitivity and specificity of 43–82% for evaluation of the T stage and sensitivity of 56% in evaluation of local lymph node involvement [21]. One potential use of PET is in the evaluation of distant organ metastasis. A meta-analysis by Kinkel designated PET as the most sensitive noninvasive imaging modality [25]. In addition, since FDG is distributed throughout the body, evaluation of the entire body may be easier than CT scan.

Another use of PET is its high specificity of 92% in the evaluation of local lymph node involvement. Identification of positive lymph nodes in regions outside the nodal basins covered by D1 and D2 lymphadenectomy can halt surgical treatment and change management. Although PET has many limitations, it could be used in situations of equivocal findings on other studies or for the evaluation of gastric cancer recurrence. Additional work is needed to find the best clinical situations for the added use of PET scan.

Conclusion

The diagnosis of gastric cancer will only continue to improve as technology advances. The ideal goal is to identify patients in a cost effective manner that have a high risk of developing gastric cancer with the hope of finding lesions at

an early stage. Better diagnostic tools combined with advances in molecular and genetic analysis will allow better tumor characterization and more individualized treatment planning. This understanding will influence staging to become a better predictor of long term overall survival and better estimate risk of recurrence and treatment failure. Patients can then be evaluated with the optimal modalities for their particular type of tumor and be given the best multimodality treatment.

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Endoscopy and Endoscopic Ultrasound Examination of the Stomach

9

Mark A. Schattner and John Chi To Wong

Abbreviations

H. pylori	*Helicobacter pylori*
UGI	Upper gastrointestinal
WLE	White light endoscopy
OLGA	Operative link of gastritis assessment
OLGIM	Operative link of gastric intestinal metaplasia
ASGE	American Society of Gastrointestinal Endoscopy
HDGC	Hereditary diffuse gastric cancer
PJS	Peutz-Jeghers syndrome
JPS	Juvenile polyposis syndrome
FAP	Familial adenomatous polyposis
HNPCC	Hereditary nonpolyposis colorectal cancer
FGP	Fundic gland polyp
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
NBI	Narrow band imaging
M-NBI	Magnification NBI
HER2	Human epidermal growth factor receptor 2
ASA	American Society of Anesthesiologists
EUS	Endoscopic ultrasound
FNA	Fine needle aspiration
MDCT	Multidetector computed tomography
MRI	Magnetic resonance imaging
FJP	Familial juvenile polyposis

Introduction

Adenocarcinoma of the stomach accounts for an estimated 7% of total new cancer diagnosis and 9% of total cancer-related deaths worldwide [1]. The role of endoscopy for gastric cancer has over time evolved to include screening, surveillance, diagnosis, staging, and treatment. This chapter will focus on the most recent approaches to endoscopic screening, surveillance, diagnosis, and staging of gastric adenocarcinoma. Endoscopic treatment by endoscopic mucosal resection (EMR) is covered in Chap. 11.

Screening and Surveillance

The incidence of gastric cancer varies considerably worldwide with a predilection for South America, Eastern Europe, Central and Eastern Asia, where some countries have adopted gastric cancer screening programs [1, 2]. In Japan, where the incidence of gastric cancer is among the highest in East Asia at over 50 men per 100,000 persons per year, photofluorography is the recommended population-based and opportunistic screening modality, which has led to a

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significant reduction in gastric cancer mortality [2–4]. A new model of screening incorporating eradication of *Helicobacter pylori (H. pylori)* with upper gastrointestinal (UGI) endoscopy has been suggested [5]. Those under 20 years of age would be tested for *H. pylori* infection and undergo eradication if affected. Individuals older than 50 years who are *H. pylori* infected would receive eradication and endoscopic examination. In Korea, the National Cancer Screening Program recommends individuals over the age of 40 undergo screening UGI endoscopy every other year, which has been shown to be cost effective, and compared to UGI series, has better sensitivity, and a higher positive predictive value [6, 7]. A recent systematic review including studies from Korea, Japan, China, and Singapore concluded endoscopy for gastric cancer in these high incident regions was more cost effective than no screening [8]. In Japan and Korea, as a result of screening, diagnosed gastric cancers are predominantly early stage lesions, which may be amenable to endoscopic treatment and have a more favorable prognosis [6].

In Western Europe and North America, where the incidence among non-Hispanic white males is 7.8 per 100,000 persons, the lower incidence renders screening not cost effective, and no population-based screening recommendations are in place [9]. However, surveillance of chronic atrophic gastritis, gastric intestinal metaplasia, or dysplasia, which represent intermediate states along the intestinal gastric carcinogenesis pathway proposed by Correa, have been suggested [10–12]. Chronic atrophic gastritis and intestinal metaplasia are recognized premalignant conditions that have an estimated annual progression rate to gastric cancer of less than 1% based on a Dutch nationwide cohort study [13]. Although the progression rate is low, worldwide one third of individuals may have chronic atrophic gastritis, while intestinal metaplasia may affect up to one quarter of the population, with more extensive disease reported in regions with higher incidence of gastric cancer [14]. At this time, white light endoscopy (WLE) cannot visually differentiate *H. pylori* gastritis from atrophy or intestinal metaplasia. While antral nodularity has >90% positive predictive value for *H. pylori* infection, the presence of visible vessels and loss of rugae folds are supportive but nonsensitive endoscopic measures of gastric atrophy [11]. Although a classification system using magnification chromoendoscopy with methylene blue had good correlation to histology, and was successfully externally validated, its use in general clinical practice is not yet widely adopted [11, 15]. Therefore, detection of these premalignant intermediates remain primarily through histological review, and when found, gastric mapping by taking at least one biopsy along the lesser and greater curvatures each of the body and antrum (3 cm from the pylorus), and one at the incisura, placed in separate vials, should be performed, as guided by the updated Sydney System [16]. Multiple biopsies are required as for both gastric atrophy and intestinal metaplasia, there is poor correlation between endoscopic and histologic diagnosis. An endoscopic interpretation of gastric atrophy had a sensitivity between 45 and 60%, based on the histological diagnosis, with lower sensitivity in patients younger than 50 years of age [17]. The sensitivity of an endoscopic diagnosis of intestinal metaplasia of the body and antrum, compared to the histological diagnosis, was worse at 24%, in a study of over 1300 patients [18]. Based on the severity and extent of intragastric atrophy or intestinal metaplasia, risk stratification per the operative link of gastritis assessment (OLGA) or operative link of gastric intestinal metaplasia (OLGIM) histological staging system can then be determined, respectively [19]. Greater extent and severity of atrophic gastritis and intestinal metaplasia are associated with an increased risk of gastric neoplasia development [20]. If extensive atrophy or intestinal metaplasia is identified, surveillance endoscopy every 3 years after diagnosis has been recommended by the European Society of Gastrointestinal Endoscopy, although there are no mortality or cost effective results from randomized studies to support these specific surveillance recommendations [11, 21]. The 2006 guidelines from the American Society of Gastrointestinal Endoscopy (ASGE) did not recommend uniform surveillance of gastric intestinal metaplasia in the United States due to weak

level of evidence, though individuals from high risk ethnicity or a family history of gastric cancer may benefit [12].

Low-grade dysplasia of the stomach has been reported to progress to gastric cancer at 5 years follow-up at a rate of 2.8–3.1 %, while high grade dysplasia progression rates are between 7 and 29 %, with differences between Asian and Western studies [13, 22]. In the absence of endoscopically defined lesions, low-grade dysplasia should have surveillance endoscopy within 1 year of diagnosis, while high grade dysplasia should have endoscopic reevaluation with extensive biopsies at 6-month to 1-year intervals [11]. EMR for low-grade dysplasia associated with a visible lesion should be considered, if clinical expertise is available, for more accurate histological staging. Kim et al. highlighted the limitations of gastric mucosal biopsy by forceps, showing that 19 % of low-grade dysplasia diagnoses were upgraded after EMR [23]. *H. pylori,* if detected, should also be eradicated, though its benefits in reversing gastric intestinal metaplasia and more severe histological disease stages are unclear [11, 12].

Other groups at risk for gastric cancer development include pernicious anemia, partial gastrectomy, and genetic syndromes such as hereditary diffuse gastric cancer (HDGC), Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), familial adenomatous polyposis (FAP), and hereditary nonpolyposis colon cancer (HNPCC). A recent systematic review and meta-analysis concluded the relative risk of gastric cancer in pernicious anemia was seven times higher compared to the general population, with a gastric cancer incidence rate of 0.27 % per year [24]. These patients are also at risk for development of type I gastric carcinoids. ASGE recommends a single upper endoscopy to identify either gastric cancer or carcinoids at time of diagnosis, but subsequent surveillance interval is unclear [12]. Similarly, surveillance of the gastric remnant in patients with surgeries for peptic ulcer disease is not routinely supported due to insufficient data. If considered, however, it should be performed 15–20 years after time of ulcer surgery, as the risk of gastric cancer development appears highest at this time [12]. Biopsies of the gastric remnant and the anastomosis are suggested [12].

Among the genetic cancer syndromes which make up roughly 5 % of total gastric cancer cases, HDGC confers one of the highest risks, with a cumulative lifetime risk of diffuse gastric cancer of approximately 80 % by 80 years of age [25]. It is characterized by loss of expression of the cell adhesion protein E-cadherin (CDH1) resulting in defective intercellular adhesion, and displays an autosomal dominant inheritance pattern [26]. Lesions usually present submucosally, as scattered microscopic foci of signet cells with intervening normal gastric mucosa. Despite its limitations, surveillance with high-definition WLE every 6 months to 1 year, beginning at 10 years earlier than the youngest affected family member or by 25 years old, is recommended for those with documented CDH1 mutation who are not candidates for total gastrectomy either by choice or fitness [27]. Testing for CDH1 mutation should be performed as recommended by the International Gastric Cancer Linkage Consortium [27]. Any endoscopically visible lesions should be sampled, and six random biopsies each at the fundus, cardia, body, body-antral transition, and antrum, totaling 30 biopsies, are recommended [27]. PJS, which is caused by mutations of the serine threonine kinase STK11, is also an autosomal dominant inherited disorder. Better recognized by the classic pigmented spots on the lips and buccal mucosa, at least 50 % of patients have gastric hamartomas. The lifetime cumulative risk of gastric cancer is estimated to be 29 %, while the relative risk has been reported to be over 200 times compared to the general population [28, 29]. Among those meeting clinical criteria for PJS, baseline upper endoscopy is suggested to start at 8 years old. If significant polyps are found, repeat surveillance endoscopy every 3 years is advised. Conversely if no polyps are detected, the next surveillance endoscopy can be delayed to 18 years of age unless symptoms arise [30]. JPS is defined as the presence of 10 or more juvenile polyps also known as hamartomas. When at least one first-degree relative have similar lesions, the term familial juvenile polyposis (FJP) is used. Germline mutations in three genes (SMAD4, BMPR1A,

and ENG) of the transforming growth factor-beta signaling pathway have been associated with JPS, which manifests as an autosomal dominant disease with high penetrance [31]. In general, upper endoscopy starts at 15 years of age, and is repeated every 1–3 years unless there are interval symptoms [31]. FAP, as a result of loss of the adenomatous polyposis coli tumor suppressor gene, confers increased risk of both colorectal and extra-colonic malignancies. While current FAP recommendations for upper endoscopy, starting at 25–30 years old, or when colectomy is considered, are primarily for surveillance of duodenal/periampullary adenomas and cancers, the stomach should also be evaluated for fundic gland polyps (FGP), adenomas and potentially gastric cancer [11, 32]. In a study of 75 consecutive FAP patients undergoing surveillance upper endoscopy, almost 90% of patients had FGP, nearly half of which were associated with dysplasia, predominantly low-grade dysplasia [33]. Larger polyp size, and more severe duodenal polyposis were associated with an increased risk of dysplasia associated FGP [33]. These authors recommended incorporating presence and degree of dysplasia associated FGP in addition to degree of duodenal polyposis to guide surveillance intervals [33]. The risk of gastric adenomas in FAP has been reported at approximately 10%, but in one study of mostly low-grade dysplastic adenomas, there was no progression to gastric cancer over a 5 year follow-up [34]. The risk of gastric cancer in HNPCC is varied from no higher than the general population to an increased lifetime risk of up to 8%, particularly among MSH1 and MSH2 mutations carriers [35–37]. Since it is the intestinal histological subtype of gastric cancer that is at higher risk of development, recent society guidelines have suggested upper endoscopy among mutation carriers starting at 30–35 years of age to screen for *H. pylori,* and, if found, its eradication with subsequent surveillance at 2–3 years intervals [38, 39]. Table 9.1 provides a summary of the above surveillance recommendations.

Diagnosis

As a result of organized screening programs, up to 50% of diagnosed gastric cancers in countries like Japan are of early stage, defined as those limited to the mucosa or submucosa regardless of lymph node involvement [40, 41]. On WLE,

Table 9.1 Summary of endoscopic surveillance recommendations for conditions associated with an increased risk of gastric cancer

At-risk conditions	Endoscopy surveillance recommendations
Pernicious anemia	At time of diagnosis, UGI WLE for increased risk of gastric cancer and type I carcinoids. Subsequent surveillance interval unclear
Partial gastrectomy	At 15–20 years after surgery, UGI WLE with biopsies of the gastric remnant and anastomosis. Subsequent surveillance interval unclear
Hereditary diffuse gastric cancer	Beginning at 10 years earlier than the youngest affected family member or by 25 years of age, UGI WLE, every 6 months to 1 year, with six random biopsies each at the fundus, cardia, body, body-antral transition, and antrum, and targeted biopsies of any endoscopically visible lesions
Peutz-Jeghers syndrome	Starting at 8 years of age using UGI WLE. If significant polyps are found, repeat surveillance endoscopy every 3 years. If no polyps are detected, next surveillance endoscopy can be delayed to 18 years of age unless symptoms arise
Juvenile polyposis syndrome	Beginning at 15 years of age with UGI WLE. Surveillance every 1–3 years unless there are interval symptoms
Familial adenomatous polyposis	Starting at 25–30 years of age for increased risk of fundic gland polyps, gastric adenomas, gastric cancer, duodenal, and periampullary adenomas and malignancies
Hereditary nonpolyposis colorectal cancer	Commencing at 30–35 years of age with UGI WLE. Subsequent surveillance at 2–3 years intervals unless symptomatic

UGI upper gastrointestinal, *WLE* white light endoscopy

early gastric cancer can be subtle, and therefore gastric contents should be suctioned away, the mucosal surface thoroughly washed of bubbles or debris, and the stomach well insufflated. The endoscopist should be attentive to interruptions of the mucosal folds, differences in mucosal color, mucosal friability, spontaneous bleeding, and changes in submucosal vessel patterns [42]. When a suspected early gastric cancer is identified, its morphology, location, size, and margins should be characterized. Current indications for EMR or endoscopic submucosal dissection (ESD) include a <2 cm nonulcerated, T1a differentiated type adenocarcinoma, with recently proposed expanded criteria [41]. Categorization of lesion morphology has been internationally standardized based on the Paris Endoscopic Classification [43]. Neoplastic lesions can be polypoid, which protrudes above the surrounding mucosa, and may have a narrow base (i.e., pedunculated) or have a base diameter similar to the top (i.e., sessile). Alternatively, nonpolypoid lesions could be slightly elevated, completely flat, or depressed compared to the surrounding mucosa [43] (Fig. 9.1). The surface morphology may also guide T staging. The findings of smooth surface protrusion or depression, slight marginal elevation, and smooth tapering of converging folds have a reported 82% positive predictive value for T1m disease when compared to pathological staging. Conversely, an irregular surface, marked marginal elevation, and abrupt cutting/fusion of converging folds had a 72% positive predictive value for T1sm disease. The overall accuracy of distinguishing T1m from T1sm lesion was 78% [44]. Lesion location can be prognostic in EMR, as those at the fundus, mid/lower body or incisura, versus the antrum, were associated with higher rates of incomplete EMR in a multicenter retrospective review of over 500 EMRs performed in Korea [45]. For advanced disease amenable to gastrectomy, tumor location, particularly in relation to the esophagogastric junction and incisura, also guides the extent of surgical resection. Lesion size is likewise prognostic in EMR, with those smaller than 3 cm achieving a higher complete resection rate than larger lesions [45]. This characteristic however has become less relevant with the advent of ESD, which allows enbloc resection of large lesions, otherwise removed piecemeal by EMR. The lateral margins of relatively flat lesions can be difficult to delineate, raising the possibility of incomplete endoscopic resections. The development of chromoendoscopy and narrow band imaging (NBI), however, has enhanced margin delineation. Chromoendoscopy is a form of enhanced imaging, whereby a dye is sprayed via the working channel on both the suspected lesion and surrounding mucosa. Indigo carmine dye is not absorbed by gastric epithelium, but instead pools in crevices highlighting differences in elevation, and mucosal irregularities.

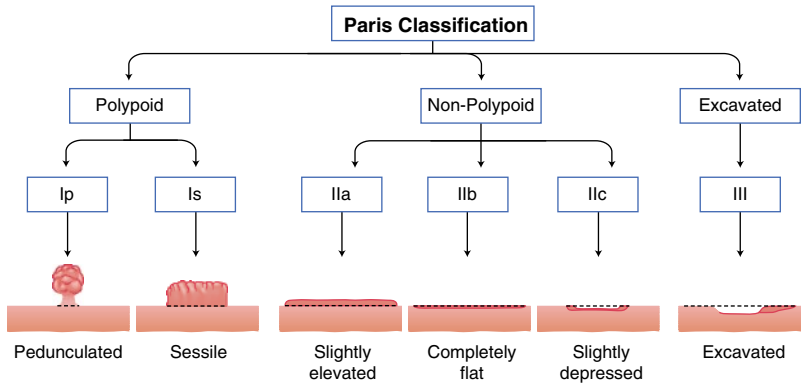

Fig. 9.1 Paris classification for superficial (type 0) neoplastic lesions of the gastrointestinal tract. Based on the endoscopic macroscopic appearance, lesions are categorized as *polypoid*/protruding: *Ip* or *Is,* or *nonpolypoid*/nonprotruding: *IIa, IIb, IIc,* or *III*

Its combined use with acetic acid was superior to either alone, or WLE alone for tumor border recognition, though a more recent study showed improved visualization among well-differentiated cancers only [46, 47]. NBI is an equipment-based form of image-enhanced endoscopy, whereby an optical filter allows light of limited wavelengths, specifically blue and green light, to illuminate the mucosa, highlighting surface and vascular architecture. Use of NBI alone to survey the gastric mucosa in its entirety is impractical due to the darkness of the lumen. Its value lies in further characterizing a lesion once identified. Normal mucosa, *H. pylori*-associated gastric atrophy, and intestinal metaplasia have distinct microsurface and microvascular features enabling differentiation from early gastric cancers [48, 49]. For example, on magnification NBI (M-NBI), the light blue crest sign on the epithelial surface has a sensitivity and specificity of approximately 90% for gastric intestinal metaplasia [50]. And the demarcation line which represents a transition of the microsurface and microvasculature characteristics on M-NBI is most indicative of cancer, and was concluded as useful to determine the lateral extent of early gastric cancer at an Asian-Pacific endoscopy consensus meeting [48, 49]. M-NBI may have better sensitivity and specificity than chromoendoscopy for the diagnosis of gastric cancers less than 5 mm [51]. Of note, however, is that undifferentiated early gastric cancers may spread subepithelially along the lamina propria, and have a normal overlying foveolar epithelium, thus limiting the utility of M-NBI [48]. Hayee et al. recently proposed a diagnostic algorithm for gastric epithelial lesions with WLE and M-NBI [49].

After visual characterization, 8–10 biopsies should be performed of the suspected neoplasia, particularly for ulcerated lesions, with standard size biopsy forceps [52]. Jumbo forceps may increase diagnostic yield, though a recent open-labeled study found for nonulcerated gastric epithelial lesions, four standard forceps (opening diameter 6.8 mm) biopsies and four jumbo forceps (opening diameter 8 mm) biopsies had similar diagnostic concordance rates when compared to the final pathology from ESD [53]. Among those with early gastric cancer likely amenable to endoscopic treatment, if *H. pylori* is detected on biopsy, its eradication may also reduce the risk of metachronous gastric cancer after endoscopic resection [54]. For more advanced cancers eligible for systemic treatment, gastric cancer biopsies should be tested for human epidermal growth factor receptor 2 (HER2) positivity, as the ToGA trial demonstrated for these patients, trastuzumab with chemotherapy resulted in longer overall survival compared to chemotherapy alone [55]. Finally, after a single lesion is identified, careful inspection for synchronous abnormalities is necessary. In one study, preoperative gastroscopy performed by endoscopists with more than 10 years of experience failed to identify 15% of synchronous multifocal gastric cancers found on surgically resected specimens, with the mean size of missed lesions (1.57 cm) significantly smaller than the detected ones (2.14 cm) [56].

The incidence of adverse events from UGI endoscopy is low, with >50% due to sedation and analgesia-related cardiopulmonary complications, reportedly occurring between 1/170 and 1/10,000 [57]. Mild events range from fluctuations in heart rate, blood pressure, and oxygen saturation to serious potentially life threatening aspiration pneumonia with respiratory distress. Risk factors include older age, higher American Society of Anesthesiologists (ASA) class, history of cardiopulmonary disease, prolonged procedure, and prone patient position [57]. The remaining complications relate to perforation, bleeding, and infection. Perforation rates range from 1/2500 to 1/11,000 and are most likely in patients with anatomical variants or abnormalities such as esophageal and duodenal diverticulum, esophageal strictures, or malignancies of the UGI tract [57]. Bleeding rates are likewise low, and the platelet threshold for diagnostic and therapeutic upper endoscopies are >20,000/mL and >50,000/mL, respectively. Preoperative management of antiplatelets and anticoagulants depends on their indications, and the procedure's risk of bleeding [58]. When bleeding from friable tumor is encountered, hemostasis is often refractory to conventional endoscopic tools, though a novel inorganic proprietary agent has shown promise

by causing mechanical tamponade, and activation of the clotting cascade [59]. Finally, infectious complications are either due to improper processing of endoscopy equipment or the procedure itself. Among UGI procedures relating to gastric cancer specifically, antibiotic prophylaxis is recommended when placing percutaneous endoscopic gastrostomies and jejunostomies [60].

Staging

Management decisions of gastric adenocarcinoma depend on accurate tumor staging. The TNM staging model developed by the American Joint Committee on Cancer and the International Union Against Cancer is based on the degree of tumor (T), nodal (N) involvement, and evidence of distant metastasis (M). T staging reflects depth of tumor invasion into the stomach wall. Tumor size does not play a role in T staging, however, is an important factor when deciding suitability of endoscopic treatment in cases of early gastric cancer. N staging describes the number of malignant nodes involved, whereas the location of nodal involvement was considered in earlier TNM classifications. M staging denotes presence or absence of distant metastatic disease. Preoperative clinical staging includes endoscopic ultrasound (EUS), possibly with fine needle aspiration (FNA), for the most accurate noninvasive locoregional T and N staging, while distant metastasis is evaluated by multidetector computed tomography (MDCT) of the chest, abdomen, and pelvis. This approach in turn risk stratifies patients to endoscopic treatment such as EMR, ESD, surgery, or systemic chemotherapy. While both the National Comprehensive Cancer Network of the United States and the European Society of Medical Oncology endorse EUS staging of nonmetastatic lesions possibly treated endoscopically, a recent Asian consensus did not include this modality for routine staging due to its T stage limitations, as discussed below [61].

Staging EUS when performed is preferably with the radial echoendoscope. The circumferential view, which is perpendicular to the shaft axis, permits assessment of wall layer involvement, abnormal lymph nodes, and tumor invasion into adjacent structures. Prior to EUS evaluation, any food contents or bubbles within the stomach should be removed or washed off, and air is suctioned from the stomach. To achieve close acoustic coupling between the echoendoscope tip and the lesion, either 300–400 cc of 0.9% isotonic saline or water can be instilled into the stomach, or a water-filled balloon placed at the echoendoscope tip can be inflated. The endoscopist should be mindful of the risk of aspiration with the patient in the left lateral decubitus position. EUS starts by positioning the probe in the antrum, instillation of water into the stomach/insufflation of the water-filled balloon, and slow withdrawal to the esophagogastric junction. With the 7.5–12-MHz echoendoscope, the normal gastric wall is represented as a 3–4-mm five-layer structure with alternating echogenicity (Fig. 9.2). The first two layers correspond to the superficial and deep mucosal layers. The third layer which is hyperechoic reflects the submucosa, while the fourth hypoechoic layer is the muscularis propria, and the outermost 5th hyperechoic layer represents the subserosal fat and serosa. Higher-frequency (>12 MHz) probes will depict the gastric wall with greater resolution with nine layers, but the depth of penetration is limited, potentially affecting nodal staging. When the lesion of interest is visualized, it is important to position the tip of the echoendoscope perpendicularly to avoid inaccurate staging from tangential views. With fine

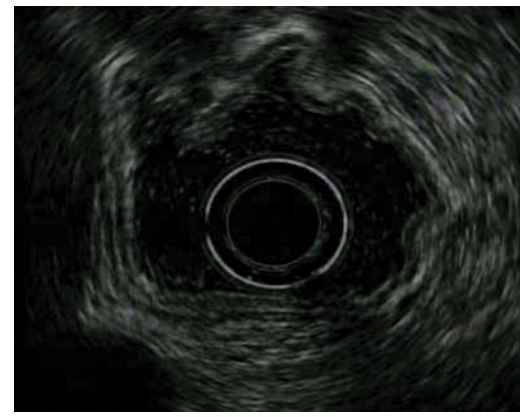

Fig. 9.2 Normal gastric wall represented as a 3–4-mm five-layer structure with alternating echogenicity

movements, the scope can be advanced, withdrawn, and torqued to provide a comprehensive assessment. Clinical T staging by EUS is categorized as:

T1a Tumor limited to the mucosa (first or second layer)

T1b Tumor limited to the submucosa (third layer). The outer margin of the hyperechoic third layer is smooth (Fig. 9.3)

T2 Tumor extends into but not through the muscularis propria (fourth layer). The outer margin of the hypoechoic fourth layer is intact (Fig. 9.4)

T3 Tumor penetrates the subserosa (fifth layer) (Fig. 9.5)

T4 Tumor invades into adjacent vascular structures (aorta or celiac axis) or organs (liver, pancreas, spleen) (Fig. 9.6)

Instead of a discrete mass, gastric cancer can alternatively present as linitis plastica from diffuse tumor infiltration causing a rigid stomach that does not insufflate well with air. On EUS, there is a markedly thickened gastric wall with loss of the normal five-layer pattern (Fig. 9.7).

Once the primary tumor has been T staged, perigastric and regional lymph nodes such as gastrohepatic ligament and celiac axis nodes are assessed. EUS features suggestive of malignant lymph nodes include size greater (vs less) than

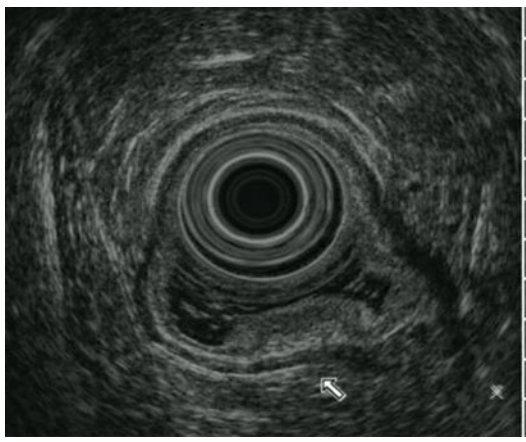

Fig. 9.3 T1b tumor limited to the submucosa (*third layer*)

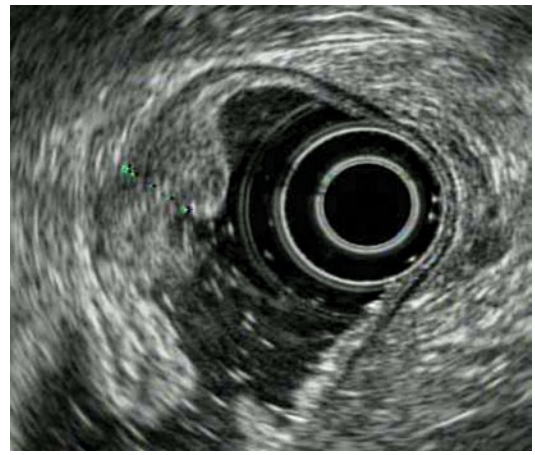

Fig. 9.4 T2 tumor extending into but not through the muscularis propria (*fourth layer*)

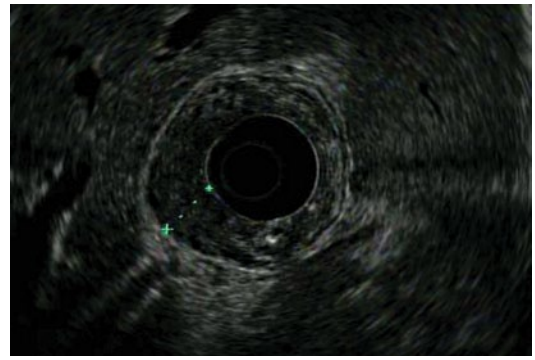

Fig. 9.5 T3 tumor penetrating subserosal connective tissue without invasion of visceral peritoneum or adjacent structures

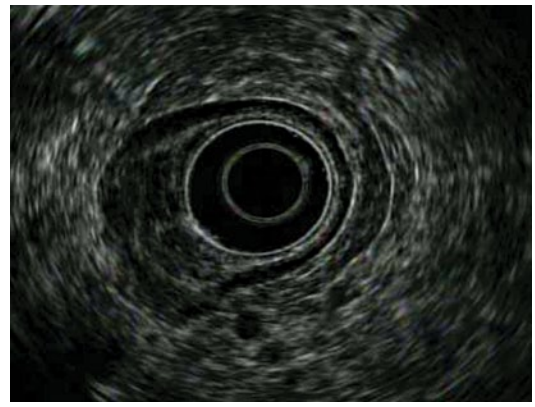

Fig. 9.6 T4a showing tumor invading serosa (visceral peritoneum)

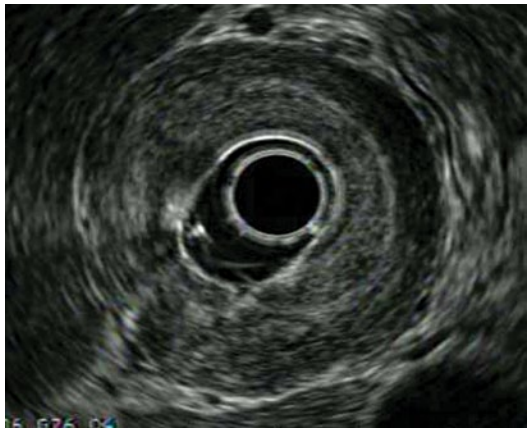

Fig. 9.7 Linitis plastica, represented on EUS as a markedly thickened gastric wall with loss of normal five-layer pattern

1 cm, circular (vs elliptical) shaped, sharp (vs irregular) margins, and hypoechogenicity (vs others). As previously noted, it is the number, not the location or proximity to the primary lesion, which dictate N staging. Cardoso et al. conducted a systematic review and meta-analysis of 22 studies between 1998 and 2009, reporting a pooled accuracy for T staging of 75% with a moderate Kappa of 0.52. EUS T staging was more accurate for T3 and T4 disease, than T1 and T2 disease [62]. Understaging can be due to microscopic infiltration, while peritumoral inflammation may result in overstaging. EUS pooled accuracy for N staging was 64%, with 74% sensitivity and 80% specificity [62]. An earlier meta-analysis likewise noted greater T stage accuracy for more advanced disease, but also demonstrated this for N staging, where the pool sensitivity of N1 disease was 58.2%, and N2 was 64.9% [63]. In comparison to other cross sectional imaging modalities, a systematic review reported the diagnostic accuracy of T staging from EUS (65–92%) was comparable to MDCT (77–88%) and magnetic resonance imaging (MRI) (71–82%) [64]. These three modalities also had similar sensitivities for N staging of between 68% for MRI to 71% for EUS and 80% for MDCT [64]. Site of disease can affect accuracy of T staging, and lesions at the cardia, lesser curvature along the upper body, and the incisura can be challenging to visualize. Further, tumor size greater than 3 cm has been associated with overstaging, while undifferentiated histology correlated to understaging in a retrospective Korean study comparing EUS T staging accuracy with EMR histology [65]. Limitation of EUS for nodal staging is primarily due to the inability to differentiate benign reactive from malignant lymph nodes. The previously described EUS criteria for malignant lymph nodes are found infrequently together. Individually, these features are not specific for cancer involvement. However when all features are present, this can confer an 80% chance of malignancy infiltrating the lymph node [66]. The likelihood of lymph node metastasis also increases with T stage [67]. Lymph nodes beyond the depth of penetration of the echoendoscope will not be detected, and this occurs more commonly for those along the greater curvature than the lesser curvature. EUS's ability to M stage is limited to assessing for disease in the left lobe of the liver, the left adrenal gland, the presence of ascites or pleural effusion, and mediastinal lymphadenopathy. EUS may detect radiographically occult liver metastases, though this is uncommon [68]. For the detection of ascites, EUS has been reported to be more sensitive than either laparoscopy/laparotomy or combined CT and ultrasound in an Asian study [69]. Found between the echoendoscope tip and external to the gastrointestinal tract and visceral organs like the liver, ascites is usually seen as a triangular anechoic space that can change shape with patient position. Finally, EUS guided FNA with a linear echoendoscope has successfully diagnosed malignant ascites, though a negative ascites fluid cytology does not exclude peritoneal carcinomatosis [70]. Endoscopists should be mindful that traversing of the EUS needle across the tumor into ascites fluid can result in false positive cytology, and seeding of the peritoneal cavity.

The type of complications associated with EUS and FNA are similar to UGI endoscopy, and include cardiopulmonary events from sedation and analgesia, perforation, bleeding, and infection [71]. In a systematic review of EUS-FNA studies mostly of pancreatic lesions, perforation, hemorrhage, infections, and post-EUS-FNA pancreatitis were reported to be 0.02% (2/10,941), 0.13% (14/10,941), 0.05% (5/10,941), and

0.44 % (36/8246), respectively [72]. To minimize risk of perforation, endoscopists should be particularly cognizant of the semi-blind nature of the cervical intubation, and the rigidity of the echo-endoscope tip compared to a standard UGI endoscope. Similar to upper endoscopy, preoperative management of antiplatelets and anticoagulants depend on their indications compared to the procedural risk of bleeding.

In summary, gastric cancer is a significant cause of global morbidity and mortality. Gastroenterology's role has expanded to encompass every stage of gastric cancer development, and endoscopists must be cognizant of the most recent evidence-based practice to support the complex multidisciplinary care provided to these patients.

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The Role of Staging Laparoscopy and Peritoneal Cytology in Gastric Cancer

10

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Once the diagnosis of gastric adenocarcinoma has been made, proper staging of the lesion is fundamental to discerning what treatment options are available and appropriate for the patient. Most patients with gastric cancer will not be candidates for curative resection, and of those who are, many will go on to develop locoregional or distant recurrences. Accurate staging practices not only provide the best opportunity to select patients who will benefit from surgery, but also help to avoid subjecting patients to the morbidity of needless laparotomies.

Similar to other solid organ malignancies, tissue biopsy, and cross-sectional imaging is imperative to diagnosis and staging. As described previously, tissue diagnosis is usually obtained through gastric endoscopy, and radiologic staging is often accomplished with a combination of endoscopic ultrasound and abdominal computed tomography (CT) with or without positron emission tomography (PET). While these tests will indentify most patients with macroscopic metastases, a significant minority of patients harbor occult macroscopic metastatic disease in the abdomen or microscopic metastatic disease in the form of positive peritoneal cytology (CYT+). As these patients have poor overall outcomes despite removal of the primary lesion, they must be identified before attempting a therapeutic resection.

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Staging Laparoscopy

In addition to the above modalities described, gastric adenocarcinoma—especially advanced lesions—should further be evaluated by staging laparoscopy. While the utility of staging laparoscopy in these patients has been addressed in the National Comprehensive Cancer Network (NCCN) gastric cancer guidelines, it remains a tool that has not been fully incorporated into the practice of American surgeons [1]. A retrospective review of Medicare data between 1998 and 2005 reported that only 7.9 % of the patients who underwent surgery for gastric cancer had undergone prior staging laparoscopy [2].

Upon insufflation of the abdomen, staging laparoscopy is traditionally performed with a 30° laparoscope introduced through a 10 mm periumbilical port, aided by a right upper quadrant helper port with or without an additional left upper quadrant helper [3]. The peritoneal surfaces, liver, diaphragm, mesentery, omentum, and remaining abdominal surfaces are examined for signs of metastatic disease. At this time, biopsies with or without the use of intraoperative ultrasound are performed. While this may be performed immediately before planned

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gastrectomy, it is more and more being used as a separate staging procedure before the initiation of neoadjuvant chemotherapy.

After a thorough physical examination, CT is the most common form of staging in gastric cancer. It has the advantages of being both noninvasive and readily available. While it has the ability to identify a significant proportion of patients with inoperable disease, it is not a perfect means of evaluation. Several earlier studies, which employed at least preoperative CT, showed that as many as 30–40% of the patients with what appeared to be operable gastric cancer were found to have visible occult metastatic disease on staging laparoscopy [4–10]. The accuracy of staging laparoscopy to detect the presence of abdominal metastases is frequently quoted to be >90% in most series [11].

Even with the advent of higher resolution CT, a 2006 study still reported 31% of the patients were found to have occult M1 gastric adenocarcinoma at staging laparoscopy [12]. In a subset of these patients evaluated in further detail, tumors found to be located in the proximal stomach, body, or antrum without evidence of lymphadenopathy were at a lower risk for occult metastases, and may be candidates to avoid staging laparoscopy. A follow-up study at the same institution showed the adjunctive role that endoscopic ultrasound may play in discriminating patients with T3-4 lesions or nodal positivity, as they are at increased risk for occult disease [13].

Additionally, finding occult metastases on laparoscopy precludes subjecting patients to the complications of undergoing a potentially curative gastrectomy, a procedure in which over one-third of patients suffer a significant complication with nearly a 5% perioperative mortality, based on national aggregate data [14]. In patients with M1 disease detected on staging laparoscopy, half will never undergo another intervention, and only 12% will require a future laparotomy [15].

Peritoneal Cytology

The utility of staging laparoscopy, however, is not limited to its ability to detect occult visible disease. Sampling the peritoneal fluid during staging laparoscopy is now commonplace, as the likely mechanism of peritoneal metastasis in gastric cancer is due to direct seeding of cancer cells shed from the primary lesion into the peritoneal fluid.

At the beginning of staging laparoscopy before manipulation of the primary tumor or biopsy of suspicious lesions, an aliquot of saline is placed into the peritoneal cavity and gently agitated. The fluid is then aspirated and traditionally sent for Papanicolaou staining to identify the presence of free tumor cells. Several newer studies have described additional genomic-level testing, but this is not standard [16, 17]. Lavage should be performed in the right and left upper quadrants to increase sensitivity [18].

Several hallmark studies have evaluated the role of peritoneal fluid evaluation and CYT+ status in patients with gastric cancer, specifically in those without evidence of other metastatic disease undergoing a potentially curative resection [19–23].

In these series, between 4.4 and 11.0% of the patients will have CYT+, even in the absence of visible M1 disease. Increasing T stage or serosal invasion of the primary lesion was frequently found to significantly raise the risk of being CYT+. This is clinically relevant as CYT+ patients universally exhibited very poor outcomes. After curative resections, most of these studies reported survival in CYT+ patients to be around 1 year, compared to over 3 years or longer (Table 10.1). Moreover, Bando et al. reported a 100% recurrence rate in CYT+ patients.

It can be concluded that CYT+ is a significant predictor of worsened survival. These findings prompted the American Joint Committee on Cancer (AJCC) to reevaluate the staging of patients with gastric cancer to include the evaluation of peritoneal cytology. Based on these data, CYT+ is now classified as an M1 disease, even in the absence of other visible disease [24]. In fact, median overall survival in patients with isolated CYT+ disease is no different than those with gross abdominal metastasis at laparoscopy [25]. Interestingly in the Ribeiro et al. series, no patients with early lesions (≤T2) were CYT+ [23]. This trend holds true in several subsequent

Table 10.1 Evaluation of CYT+ in patients undergoing curative resection for gastric cancer

Study	Year published	N Cyt+ (%)	Factors associated with CYT+	Survival after resection	Comments
Bonenkamp [19]	1996	20 (4.4)	T stage, presence of serosal invasion, nodal status	CYT−: >3 years CYT+: 1.1 year	
Bando [20]	1999	30 (7.3)	Tumor histology, CEA, CA 19−9	CYT−: NR CYT+: 1 year 37%, 5 year 0%	100% of CYT+ developed recurrence
Kodera [21]	1999	10 (11.0)	Tumor size, nodal status, clinical stage	CYT−: NR CYT+: 386 days	CYT+ most significant multivariate predictor of survival
Bentrem [22]	2005	24 (6.5)	T stage, clinical stage	CYT−: 98.5 months CYT+ 14.8 months	CYT+ most significant multivariate predictor of survival
Ribeiro [23]	2006	15 (6.8)	T stage, clinical stage	CYT−: 61 months CYT+10.5 months	All CYT+ were≥T3

evaluations; similar to evidence presented for staging laparoscopy in general, peritoneal fluid sampling has a lesser effect on therapeutic planning in early stage gastric cancer and may be reserved for only those who present with advanced lesions (Fig. 10.1).

Treating patients with $M1_{CYT+}$ disease with chemotherapy has been shown to improve survival (Table 10.2). Badgwell et al. reported a 7-month survival gain (total 16.2 months) over palliation alone [25]. A subsequent trial by Lorenzen et al. showed that 37% of CYT+ patients

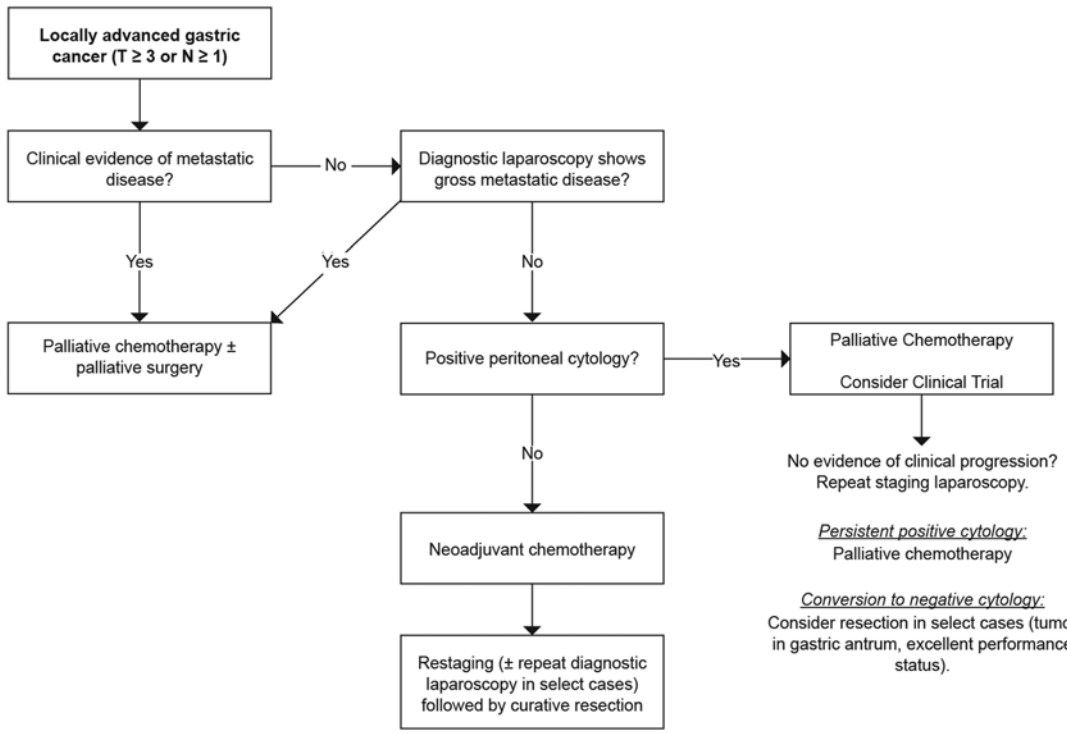

Fig. 10.1 Proposed algorithm for use of staging laparoscopy and peritoneal cytology evaluation in patients with gastric cancer. (From [28]. Reprinted with permission from John Wiley and Sons)

Table 10.2 Outcomes in CYT+ patients after treatment

Study	Year	$M1_{CYT+}$ (N)	Key findings
Badgwell [25]	2008	39	Improved survival with chemotherapy compared to palliation only (16.2 months vs. 7.2) No difference in survival between $M1_{CYT+}$ and gross metastatic disease
Okabe [31]	2009	10	In selected patients with complete peritoneal clearance, may obtain durable cure with R0 resection
Kuramoto [31]	2009	88	Extensive intraoperative peritoneal lavage with intraperitoneal chemotherapy greatly improved survival in locally resectable $M1_{CYT+}$ patients
Lorenzen [26]	2010	NR	37% of patients converted from CYT+ to CYT− with chemotherapy 24% of patients converted from CYT− to CYT+ while on chemotherapy
Mezhir [32]	2011	93	Conversion to CYT− improved survival by 1.1 years (total 2.5 years). No survival improvement in converters who had subsequent R0 resection

were able to convert to CYT−; these responders had improved median survival compared to those who were persistently CYT+ (36.1 months vs 9.2 months) [26] and was again confirmed by Mezhir et al. [27]. Of note in the Lorenzen study however, is that even though the primary lesion may become resectable, perhaps as high as a quarter of the patients with locally advanced gastric lesions may progress from CYT− to CYT+ despite chemotherapy.

Treatment of CYT+ disease remains a novel area of focus [28, 29]. In addition to traditional chemotherapy administration, intraperitoneal chemotherapy has been evaluated. The theory behind this treatment is to eradicate free tumor cells and prevent them from seeding the peritoneum and abdominal viscera. A meta-analysis of three trials showed a trend towards improved overall survival (HR 0.70, $p<0.008$), putting this forward as a potential treatment while awaiting further studies [29]. On a more basic hypothesis, a single, but intriguing randomized controlled trial by Kuramoto et al. has evaluated the effect of simply diluting out the free tumor cells by means of extensive intraoperative lavage [30]. In patients with locally resectable CYT+ disease who underwent surgery alone, 5 year overall survival was 0%, compared to 4.6% in those who received surgery with intraoperative peritoneal chemotherapy. This was in stark comparison to the 43.8% survival in the patients who received surgery, 10 L saline lavage of the peritoneum, and intraperitoneal chemotherapy.

Subsequent resection in these patients with complete peritoneal response with chemotherapy remains unclear. In a small subset of patients who converted from CYT+ to CYT− and underwent attempted curative resection, there was no improvement in median disease specific survival when compared to converters who did not undergo resection [27]. A small study by Okabe et al. does however report a survival advantage in highly selected complete responders who go on to obtain an R0 resection. This remains experimental, and at most institutions, patients with $M1_{CYT+}$ disease will only undergo resection for palliation of symptoms.

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Part III

Gastric Resection and Postoperative Management

Endoscopic Resection for Gastric Cancer

11

Yoshihiro Komatsu and Blair Anderson Jobe

Introduction

Gastric cancer is the one of the most common cancers worldwide [1]. In the USA, the incidence rate of gastric cancer has significantly declined over the past 50 years. Today, approximately 22,220 patients are diagnosed with gastric cancer annually and 10,990 are expected to die from the disease [2]. Although the incidence rate has declined, the mortality rate remains high with a 25 % 5-year survival rate for all stages combined [3]. This reflects prevalence of advanced disease at presentation and aggressive biology. The majority of gastric cancers are adenocarcinoma and the diagnosis is usually confirmed by endoscopic examination and histologic evaluation. The clinical manifestation of early gastric cancer is vague including asymptomatic, dyspepsia, epigastric pain, early satiety, or nausea. Thus, the detection of early stage disease by screening and surveillance with endoscopy is critical. With the high incidence of gastric cancer in Asia, the majority of early gastric cancers are detected through screening including photofluorography and endoscopy [4].

Currently, early gastric cancer is defined when it invades no deeper than the submucosa, regardless of lymph node metastasis (T1, any N) [5, 6]. The overall 5-year survival rate for early stage gastric cancer is over 90 %, nearly 100 % for mucosal tumors, and 80–90 % for submucosal tumors [5, 7–9]. Among the early gastric adenocarcinomas, the incidence of lymph node metastasis is 2–3 % for intramucosal tumors and 20–30 % for submucosal tumors [10]. Therefore, neoplastic lesions that invade into lamina propria but are confined to the mucosa can be a reasonable target for endoscopic resection [11]. The major advantage of endoscopic resection is its ability to provide complete histopathological evaluation of the neoplastic lesion. Pathological assessment, including the depth of the lesion, degree of cellular differentiation, and extent of lymphovascular invasion, facilitates the risk stratification of lymph node metastasis and refinement of further treatment [12].

Macroscopic Classification of Early Gastric Cancer

Since the incidence ofgastric cancer is extremely high in Japan, a macroscopic classification has been established in order to codify endoscopic description of a given lesion [6]. The Japanese Gastric Cancer Association introduced the

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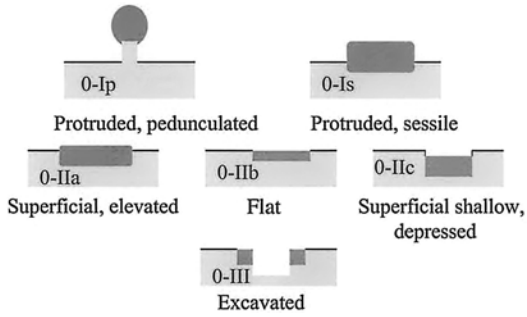

Fig. 11.1 Schematic representation of the major variants of type-0 neoplastic lesions of the digestive tract: polypoid (Ip and Is), nonpolypoid (IIa, IIb, and IIc), nonpolypoid and excavated (III). (From [13]. Reprinted with permission from Elsevier Limited)

classification in which lesions were categorized into six types (0–5) based on the macroscopic appearance [6]. Type-0 lesions represent a superficial tumor that invades no deeper than submucosal layer and are further subclassified into several subtypes. Based on the classification, the Paris system was proposed to develop universal consensus in 2002 [13] (Fig. 11.1). Type 0-II lesions account for 58 % of tumors with a diameter smaller than 5 mm [14]. Type 0-I and IIa lesions are associated with a low risk of lymph node metastasis [15].

Clinical Staging

The patients who are considered for endoscopic resection of gastric cancer should undergo endoscopic ultrasound (EUS), computed tomography, and F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) for clinical staging. Patients with no or low risk of lymph node metastasis are ideal candidates for endoscopic resection.

In a recent meta-analysis including 22 studies, Cardoso and colleagues reported that the accuracy of EUS for T staging was 75 %, and EUS was most accurate for T3 tumors, followed by T4, T1, and T2. In addition, the accuracy, sensitivity, and specificity of EUS for N staging were 64, 74, and 80 %, respectively [16]. Also, studies have reported that the reliability of EUS to evaluate the depth of T1 tumor invasion remains insufficient even with a high-frequency probe (12–20 MHz) [17, 18]. Based on these findings, EUS is not accurate enough to determine the depth of tumor especially for the patient with superficial lesions. Thus, the major role of EUS is to exclude obvious lymph node involvement.

On the other hand, previous studies have shown that the specificity of FDG-PET to detect lymph node involvement and distant metastasis was high (89–100 and 35–74 %, respectively), whereas the sensitivity was varied (21–40 and 35–74 %, respectively) [19–21]. Koga et al. have demonstrated that physiological FDG uptake in stomach varies depending on the location of stomach [22]. Other studies have reported that the FDG uptake is low in the early gastric cancer as well as signet-ring cell carcinoma and poorly differentiated carcinoma [23, 24]. Therefore, the major role of FDG-PET in gastric cancer is to evaluate for distant metastasis.

Because T staging is limited using EUS and FDG-PET, the final staging can only be done through histological analysis. Endoscopic resection is most commonly used for the purpose of T staging. To assess the relationship between depth of invasion and lymph node involvement, the mucosal and submucosal layers have been subdivided into thirds with each third going deeper into gastric wall. Intramucosal (m) and submucosal (sm) cancers have a total of six different layers of invasion: m1–m3 (m1 is limited to the epithelial layer; m2 invades into the lamina propria; m3 invades into but not through the muscularis mucosa) and sm1–sm3 (thirds of the submucosa) (Fig. 11.2).

Indications for Endoscopic Resection

Currently, endoscopic resection for early gastric cancer has been widely accepted and well established in Japan.Initial criteria for endoscopic resection of early gastric cancer were established based on the technical limitations of en bloc endoscopicmucosal resection (EMR) for removing neoplastic lesions larger than 20 mm in diameter [11, 25]. Therefore, the present guidelines for indication ofEMR are: (1) differentiated (well and/

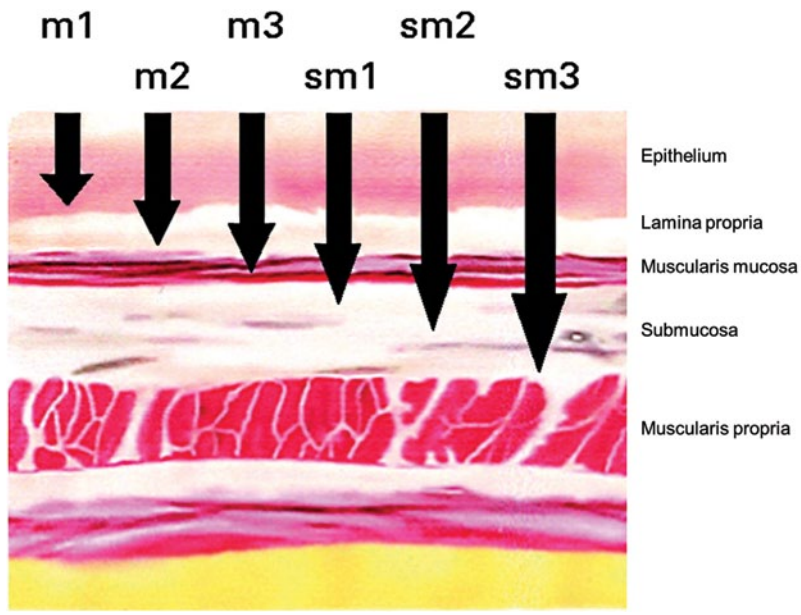

Fig. 11.2 Subdivision of the mucosa and submucosa. For the staging purpose, the mucosal layers are subdivided into thirds with each third going deeper into the gastric wall. (Modified from Soetikno et al. [30], with permission from American Society of Clinical Oncology)

or moderately differentiated and/or papillary adenocarcinoma) histology, (2) no ulcerative findings and a depth of invasion that is confined to the mucosa (T1a), (3) a tumor diameter ≤20 mm, and (4) absence of lymphatic-vascular involvement [26]. Endoscopic resection is not indicated for poorly differentiated adenocarcinoma or signet-ring cell carcinoma.

However, clinical observations have suggested that the absolute criteria may be too strict and can lead to unnecessary gastrectomy. To expand the criteria with the establishment of endoscopic submucosal dissection (ESD) technique, Gotoda and colleagues analyzed more than 5000 patients who underwent gastrectomy with meticulous D2 lymphadenectomy to define the risk of lymph node metastasis in specific groups of patients with early gastric cancer [27]. According to the study, there were four subgroups of patients with early gastric cancer with no risk of lymph node metastasis: (1) differentiated (well and/or moderately differentiated and/or papillary adenocarcinoma) intramucosal adenocarcinoma without lymphatic-vascular invasion, regardless of ulceration status and a tumor size <30 mm (n=1230; 95% CI, 0–0.3%), (2) differentiated intraluminal adenocarcinoma without lymphatic-vascular invasion, without ulceration, regardless of tumor size (n=929; 95% CI, 0–0.4%), (3) undifferentiated (poorly differentiated adenocarcinoma and/or signet-ring cell carcinoma) intramucosal adenocarcinoma without lymphatic-vascular invasion, without ulceration, and a tumor size <30 mm (n=141; 95% CI, 0–2.6%), and (4) differentiated minute submucosal adenocarcinoma (sm1) without lymphatic-vascular invasion, and a tumor size <30 mm (n=145; 95% CI, 0–2.5%) [27]. Despite these data,endoscopic therapy for patients with undifferentiated intramucosal carcinoma has been considered controversial. However, recent studies have shown that no lymph node metastasis was identified in 310 patients with undifferentiated intramucosal carcinoma without ulceration or lymphatic-vascular invasion, and tumor size <20 mm (95% CI, 0–0.96%) [28, 29], suggesting that early gastric cancer with undifferentiated histology can be included in the spectrum of endoscopic resection. Based on these results, proposed indications for endoscopic resection for early gastric cancer have been expanded

Table 11.1 Proposed expanded criteria for endoscopic mucosal resection (*EMR*) and endoscopic submucosal dissection (*ESD*) for early gastric cancer

Guideline criteria (EMR)	Proposed expanded criteria (ESD)
Intramucosal (m) tumor	Intramucosal (m) tumor
Elevated lesion ≤20 mm	Without ulceration >20 mm
Flat/depressed lesion ≤10 mm without ulceration	With ulceration ≤30 mm
No indication for submucosal tumor	Submucosal (sm1) ≤30 mm
Moderately or well-differentiated adenocarcinoma	
No lymphatic-vascular invasion	

to include intramucosal (m1–3) differentiated adenocarcinoma without ulceration regardless of size or with ulceration ≤30 mm in diameter, and the superficial third submucosal (sm1) differentiated adenocarcinoma ≤30 mm in diameter [30] (Table 11.1). In addition, these tumors should be without lymphatic-vascular involvement.

Endoscopic Resection Techniques: EMR and ESD

EMR and ESD were established for the minimally invasive endoscopic removal of benign and early malignant lesions in the gastrointestinal (GI) tract. EMR is typically used for removal of lesions smaller than 20 mm or piecemeal removal of larger lesions. ESD is utilized for en bloc resection of lesions greater than 20 mm. En bloc resection is ideal because of the higher risk of disease recurrence with piecemeal removal due to incomplete resection and compromised histological assessment secondary to involved radial margins [31].

Endoscopic Mucosal Resection

Several techniques of EMR have been introduced including the injection-assisted technique, the cap resection technique, and the ligate-and-cut technique (Fig. 11.3).

Injection-assisted EMR starts with injection of a solution into the submucosal layer under the lesion, creating a "safety cushion." This cushion lifts the lesion to facilitate its removal and prevent complications such as perforation caused by mechanical and electrocautery damage to deeper layers. A polypectomy snare is used through a single-channel endoscope to snare the lesion (Fig. 11.3a). The injected solutions, especially normal saline, spread out into the submucosal space within a few minutes and repeat injections

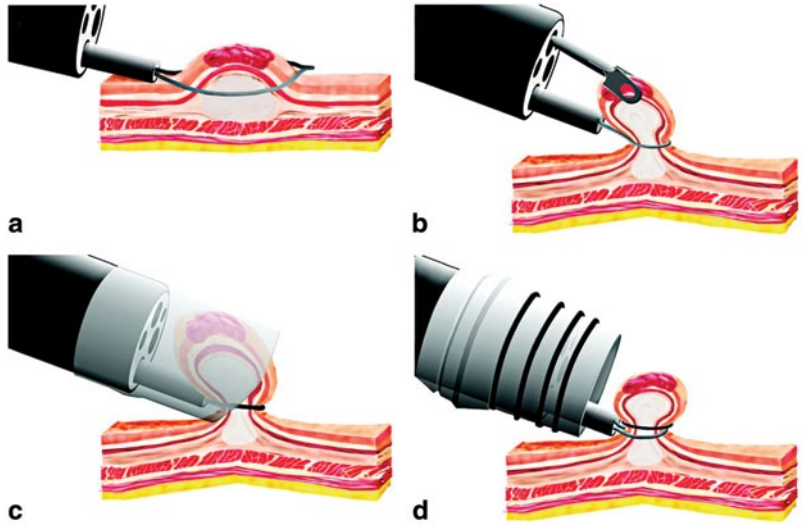

Fig. 11.3 Four types of commonly used endoscopic mucosal resection (*EMR*) techniques. **a** The inject-and-cut technique. **b** The inject-lift-cut technique. **c** The EMR with cap technique. **d** The EMR with ligation technique. (From Soetikno et al. [30]. Reprinted with permission from American Society of Clinical Oncology)

may be required for successful EMR. In addition, the marking of the target tumor margin using electrocautery may be considered to identify the accurate resection margin after the submucosal injection changes the shape of the lesion.

The strip biopsy technique was developed as an application of injection technique. In this method, a double-channel endoscope is used in order to snare the lesion while it is grabbed and pulled toward the endoscope with a grasper [32] (Fig. 11.3b). As a variation of this technique, Kondo et al. reported EMR of large gastric lesions with countertraction of the lesion by grasping forceps placing through a percutaneous gastrostomy [33].

Currently, the endoscopic cap resection technique (EMR-C) and the endoscopic ligate-and-cut technique (EMR-L) are commonly performed in the USA. Between these techniques, a randomized trial has demonstrated similar efficacy and safety for EMR of early-stage esophageal cancers [34]. EMR-C also uses submucosal injection to lift the target lesion. Dedicated mucosectomy devices that use a plastic cap with rim and a specialized crescent-shaped electrocautery snare have been developed [35]. The snare must be opened and placed on the internal circumference rim at the tip of cap, which is attached on the end of the forward-viewing endoscope. Once the endoscope is positioned over the lesion, suction is applied to retract the lesion into the cap, and the snare is closed to capture the base of the pseudopolyp. The lesion is then resected with a standard snare excision (Fig. 11.3c). Different sized and shaped caps are available based on the tumor size and location (Fig. 11.4). The straight caps are commonly used for the lesions in the stomach and colon and the oblique-shaped caps are usually used in the esophagus where a tangential approach is often required [35].

EMR-L uses a cap attachment with band ligation device (Fig. 11.3d). The device is positioned over the target lesion with or without prior submucosal injection. Suction is applied to retract the lesion into the cap and the band is deployed underneath it creating a pseudopolyp. The pseudopolyp is then resected at its base with an electrocautery snare [36]. The band has enough contractile force to squeeze the mucosal and submucosal layers, but it is not strong enough to capture the muscularis propria. A multiband ligation system was developed to avoid the repeated withdrawal and insertion of the endoscope for band ligation and subsequent resection (EMR-MBL). In our practice, a multiband mucosectomy device (Duette^{TM}, Cook Medical Inc., Bloomington, IN) is commonly used (Fig. 11.5). This device includes a specially designed six-band ligator, through which a polypectomy snare can be passed, and the band ligation and subsequent resection can be performed in series without withdrawal of the endoscope.

The advantages of EMR-C and EMR-L/EMR-MBL techniques would be their simplicity, which only requires the use of a standard endoscope. However, the limitation of EMR is that it cannot be used to remove en bloc lesions larger than 2 cm. Again, piecemeal resection for lesions larger than 2 cm leads to a higher risk of local recurrence and insufficient pathological staging [31, 37]. Thus, a technique to remove larger lesions en bloc was developed [38, 39].

Fig. 11.4 Different size and shape of the caps utilized for endoscopic mucosal resection (*EMR*). On the *left*; straight hard cap. In the *middle*, oblique-shaped soft cap. On the *right*; oblique-shaped hard cap. (Permission for use granted by Olympus Medical Systems Corp., Japan)

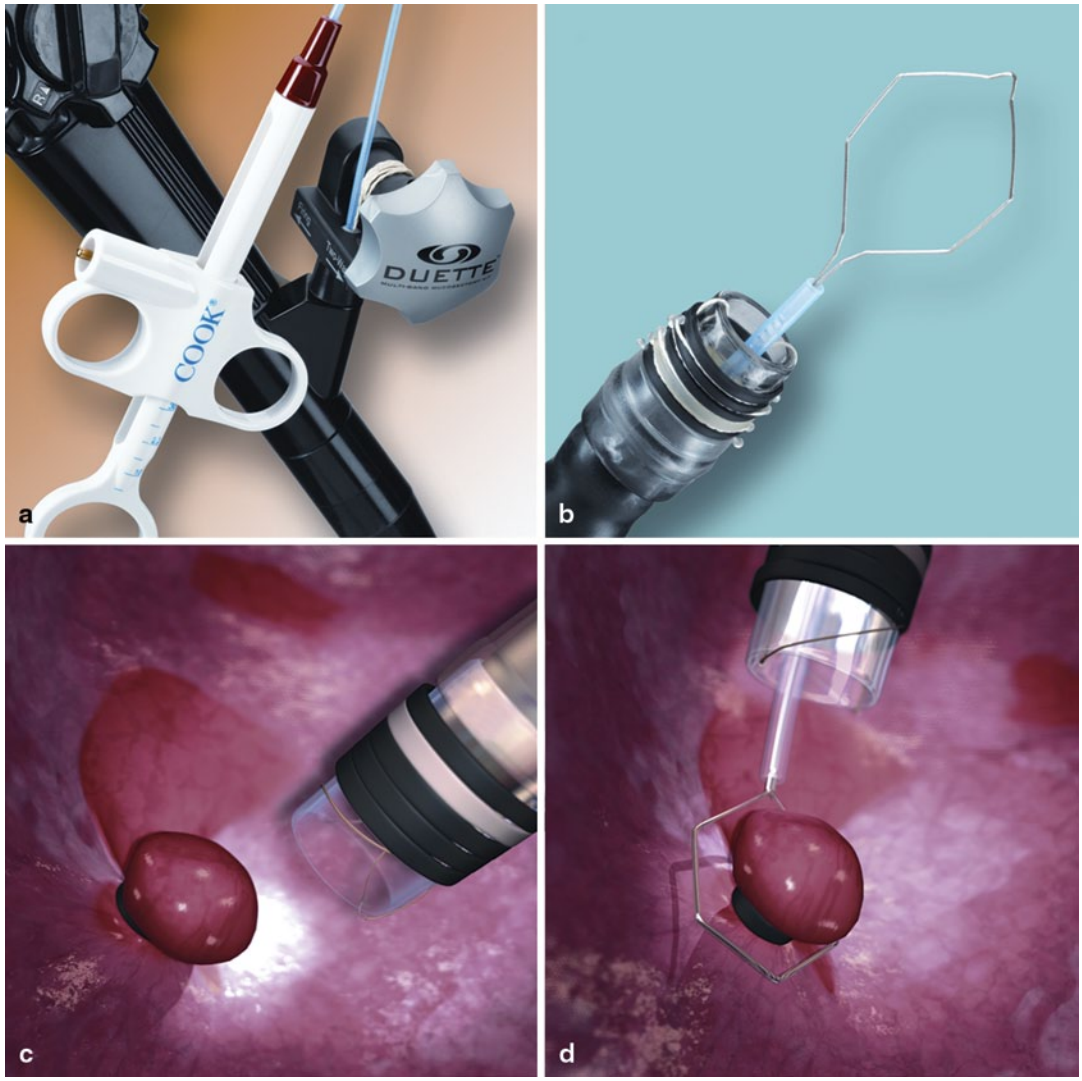

Fig. 11.5 Multiband mucosectomy device. **a** and **b** Multiband mucosectomy kit. **c** Pseudopolyp created by ligation. **d** Snare wire is applied on its base to resect. (Permission for use granted by Cook Medical Incorporated, Bloomington, Indiana)

Endoscopic Submucosal Dissection

ESD was developed in Japan for en blocremoval of lesions larger than 2 cm in diameter [38–40]. It is an advanced endoscopic resection technique, which involves direct dissection of the submucosal layer using a specialized needle knife. Since the first introduction of ESD using an insulation-tipped knife in Japan [39], various types of needle knives have been developed and introduced into practice (Fig. 11.6). En bloc resection of lesion allows more accurate pathological evaluation of the lateral and radial margins and reduces the risk of local recurrence [41, 42]. ESD requires several steps, and only carbon dioxide insufflation should be used (Fig. 11.7). First, the margin of the lesion (normal mucosa around the lesion) is marked by electrocautery, which is critical for the success of en bloc resection of large lesions. Then, submucosal injection is used to lift the

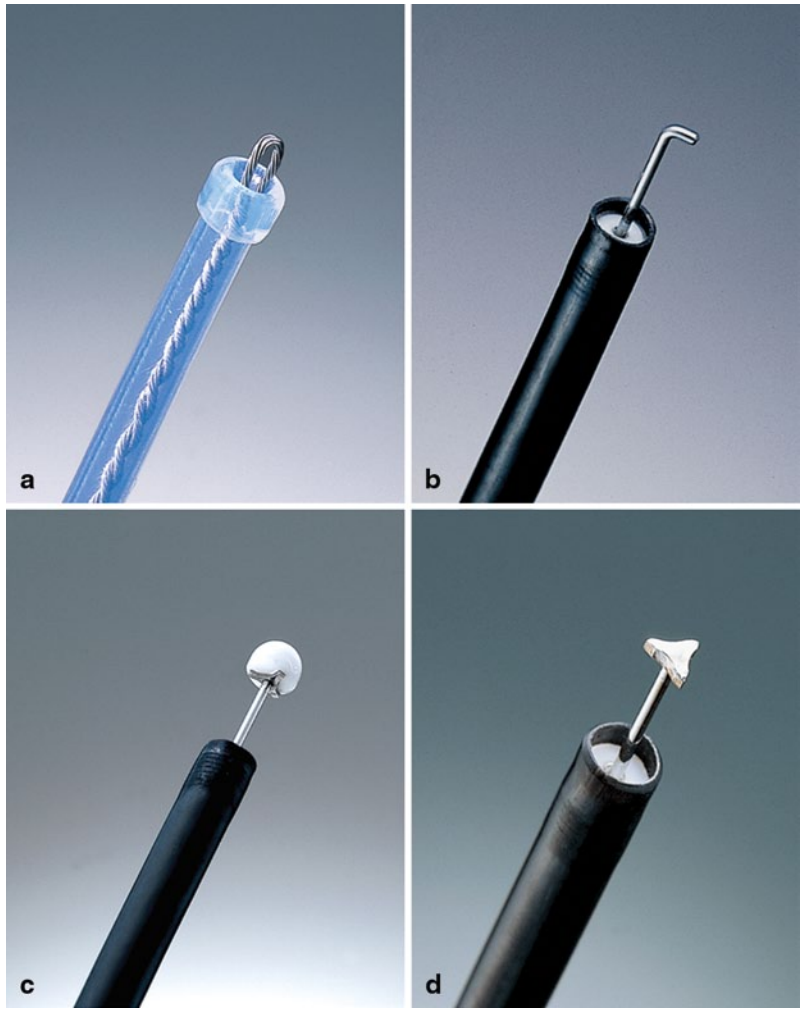

Fig. 11.6 Needle knives used for endoscopic submucosal dissection (*ESD*). **a** Flex knife. **b** Hook knife. **c** Insulation-tipped knife (IT knife2). **d** Triangle-tip knife (TT knife). (Permission for use granted by Olympus Medical Systems Corp., Japan)

lesion. In practice, it is preferred to use sodium hyaluronate solution (approximately 0.5% solution) mixed with epinephrine (0.01 mg/ml) and indigo carmine (0.04 mg/ml), which remains in the submucosal space for a longer period compared with other solutions such as saline and glycerol [43, 44]. Next, the mucosa is incised for a distance of 5 mm outside of the radial margin markings using a needle knife. Once the access to the submucosal space is created, appropriate tension and counter-tension are maintained using cap placed on the insertion tube of the endoscope, which is inserted into submucosal space. The dissection is performed using a needle knife by dissecting submucosal tissues and bridging vessels within the submucosal space. Large vessels should be cauterized using hemostatic forceps. At the completion of the procedure, the lesion should be removed en bloc regardless of its size, preserving a thin layer of submucosa (sm3) overlying the muscularis propria. Hemostasis should be completed by coagulating visible vessels with hemostatic forceps to prevent post-procedure bleeding. To maintain adequate countertraction between the mucosal–submucosal complex and muscularis propria, it is important to consider

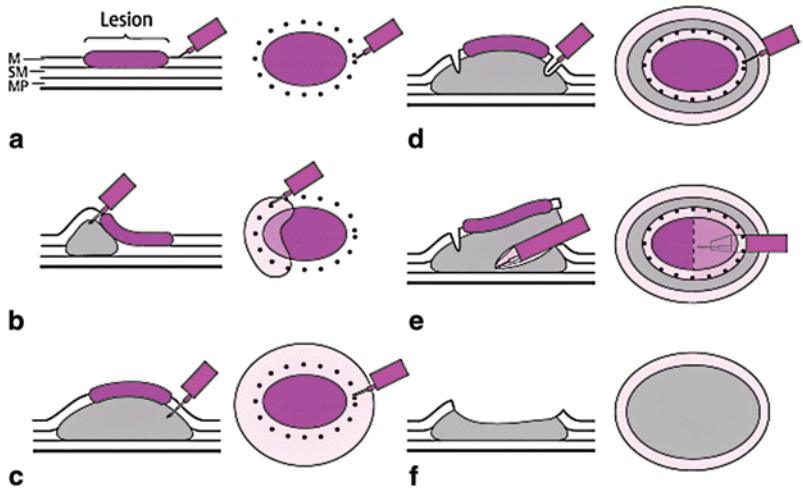

Fig. 11.7 Technique used for endoscopic submucosal dissection (*ESD*). **a** Mucosal markings. **b** Submucosal injection of solution. **c** Complete elevation of the lesion by injecting solution into the submucosal space. **d** Mucosal incision with a needle knife at the distal and proximal extent of the tumor. **e** Submucosal dissection/tunnel with a needle knife with cap-attached endoscope, followed by division of the flanking mucosa. **f** Completion of the en bloc resection of the lesion. *M* mucosa, *SM* submucosa, *MP* muscularis propria. (From Yamamoto et al. [40]. Reprinted with permission from Thieme)

how to make the initial mucosal incisions. Partial mucosalincisions should be made first at the most proximal and distal aspects of the tumor; a submucosal tunnel is then created, thereby linking these two openings and exploiting the added countertraction offered by the intact mucosa on the sides flanking the tunnel. The flanking mucosa is then cut, thereby freeing the tumor. It is important to work from proximal to distal locations so that the dissected portion of the tumor can be "pulled" out of the way by gravity.

Pathological Staging

The proper pathological assessment of the resected specimen is crucial for an accurate diagnosis andstratification of the risk of metastasis. The specimen should be properly oriented immediately after endoscopic removal before it is immersed in formalin solution. The specimen should be circumferentially pinned flat on to a cork or rubber plate with the mucosal side facing out. After fixation in formalin, the specimen should be sectioned serially at 2-mm interval parallel to a line that includes the closest resection margin of the specimen in order to assess both radial and vertical margins. The depth of the tumor invasion (T) is evaluated along with the degree of cellular differentiation and lymphatic-vascular involvement [6, 45].

Post-procedure Management and Complications

Patients should be observed in the post-anesthesia care unit until they awake.For patients who undergo EMR, no further tests, such as a chest radiograph or complete blood count, are required unless there is an evidence of bleeding or perforation; patients who undergo EMR can be discharged on the same day of the procedure. For the patients who undergo ESD, a chest X-ray, blood tests, or upper GI contrast study may be required depending on the intraoperative findings and patient condition.

The complications of endoscopic resection for early gastric cancer include bleeding, pain, and perforation. Post-endoscopic resection pain is usually mild and can be controlled by medication including topical anesthetic agents such as liquid

xylocaine. Patients are typically fasted for 12 h after the procedure and followed by a soft diet for 1 week. Nonsteroidal anti-inflammatory agents should be avoided for a minimum of 6 weeks. Proton pump inhibitor therapy is given twice a day for 8 weeks [46]. H2 blocker and cytoprotective agents, such as sucralfate, can also be added. The most common complication is bleeding, occurring in up to 8% of patients with EMR and in up to 7% of patients with ESD [47]. Bleeding usually occurs during the procedure or within 24 h after the procedure commonly at resection sites in the upper third of the stomach. Delayed bleeding may occur with the manifestation of hematemesis or melena at 0–30 days after the procedure, which should be treated with emergency endoscopy after fluid resuscitation using hemostatic forceps, argon laser, endoclips, or injection of epinephrine solution [48]. Delayed bleeding is more common with ESD, which likely occurs after resection of large (>30 mm) lesions located in the middle or lower third of stomach [49]. Perforation is uncommon during EMR. The risk of perforation during ESD is 4% [47]. Small perforations can be closed with endoclips but larger perforations may require emergent surgery to prevent peritonitis.

Outcomes of Endoscopic Resection

The outcomes of EMR for early gastric cancer have been extensively investigated in Japan. Based on the successfuloutcomes observed from these studies, EMR became the standard treatment of early gastric cancer in Japan [50, 51]. Kojima et al. reviewed the outcomes of 1832 patients with early gastric cancer who underwent EMR from 12 major institutions in Japan, which demonstrated that the disease-specific survival rate was 99% with minimal complication rates (bleeding 1.4%, perforation 0.5%). However, not all studies reported long-term outcomes. From the report, the risk of local recurrence was relatively high, which varied from 2 to 35%, especially when en bloc resection was not achieved or the resection margins were not free from disease [52]. Continued endoscopic surveillance is a critical component to endoscopic resection of gastric malignancy and the patient should be informed of the possibility of the need for further intervention. In a recent large prospective study involving patients with early gastric cancer comparing the long-term outcomes of endoscopic resection between patients who were treated with the guideline criteria ($n=635$) and patients who were treated with the extended criteria ($n=625$), Gotoda and colleagues demonstrated that there was no significant difference in the 5-year survival (92.4 and 93.4%, respectively) or local recurrence rates [53]. These findings suggest that the extended criteria for the endoscopic resection of early gastric cancer are safe, effective, and applicable (Table 11.1).

Conclusions

Endoscopic resection is a minimally invasive, organ-preserving approach to treat premalignancy or early-stage cancer in the GI tract. Accurate endoscopic examination with complete histological assessment and staging is critical to determine whether definitive endoscopic resection is appropriate for a patient with gastric cancer. Selected patients with early gastric cancer based on the guideline criteria can be managed endoscopically with successful outcomes. Currently, EMR is performed for lesions smaller than 20 mm. En bloc resection is preferred because of the high risk of local recurrence after piecemeal resection, therefore ESD should be considered for lesions larger than 20 mm. Early results have been encouraging so that the indication for endoscopic resection can be expanded. Further prospective studies to justify the extended criteria as well as the actual benefit of ESD are required.

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12 Methods of Reconstruction—BI, BII, Roux-en-Y, Jejunal Interposition, Proximal Gastrectomy and Pouch Reconstruction

Daniel E. Stange and Jürgen Weitz

Introduction

Removal of parts or the whole stomach due to stomach cancer or benign diseases is normally followed by the reconstruction of the digestive tract continuity (Fig. 12.1) [1]. Several different approaches have been described to achieve this goal [2–9]. Decisive factors that have to be taken into account when deciding on the type of reconstruction include functional outcome, the morbidity rate of the procedure, and the life-time expectancy of the patient. The functional outcome includes the possible postoperative diet and resulting nutritional status of the patient and his quality of life. The morbidity rate as well as the associated mortality rate depends on the complexity of the procedure, i.e., the formation of a pouch or the inclusion of a duodenal anastomosis. The life-time expectancy needs to be balanced with the morbidity rate, favoring a rather simple reconstruction for patients presenting with advanced diseases. The availability of randomized controlled trials (RCTs) evaluating different aspects of the competing reconstruction techniques enables shared decision making, taking into account the individual case and evidence-based surgery.

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Reconstruction Following Distal Gastrectomy

Methods for Reconstruction

Distal gastrectomy (Fig. 12.1c) includes all procedures that leave the esophago-gastral junction intact, i.e., antrectomy, 2/3 and 4/5 gastric resections. The following reconstructions are most frequently used:

- Billroth I, characterized by a gastro-duodenal anastomosis
- Billroth II, characterized by a gastro-jejunostomy of the remaining stomach to the first jejunal loop
- Roux-en-Y, characterized by a gastro-jejunostomy of the remaining stomach to an excluded jejunal limb and an end to side jejuno-jejunostomy between the excluded jejunum to the first jejunal loop

Billroth I

The reconstruction according to Billroth I (BI) was first performed in 1881 and is characterized by an anastomosis between the remaining stomach and the duodenum (Fig. 12.2a) [10]. Potential advantages of this procedure include the maintenance of a physiological gastro-duodenal passage of the food. Nevertheless, the BI reconstruction is restricted to cases with a limited resection of the distal stomach due to the restricted mobilization possibilities of the duodenum and remaining stomach to establish a tension-free anastomosis. Furthermore, a limited distal resection is contra-

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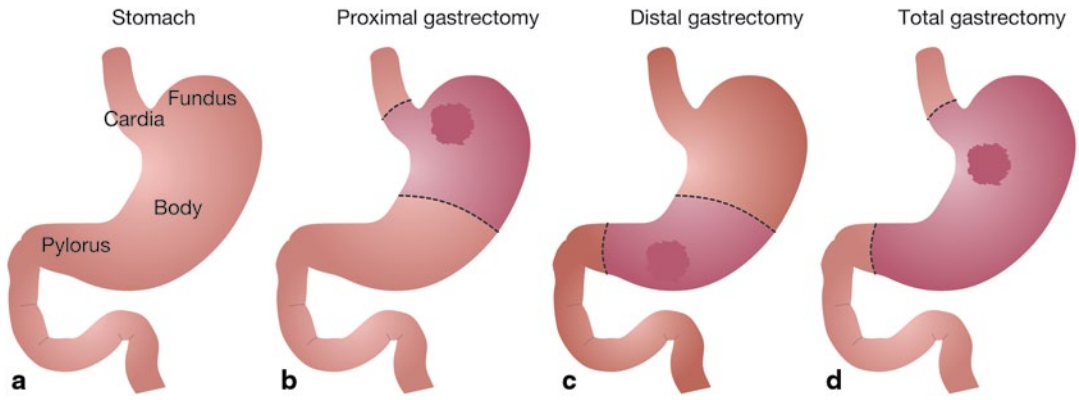

Fig. 12.1 Anatomy and resection procedures of the stomach. **a** The four sections of the human stomach. **b** Schematic drawing of proximal gastrectomy. **c** Schematic drawing of distal gastrectomy. **d** Schematic drawing of total gastrectomy

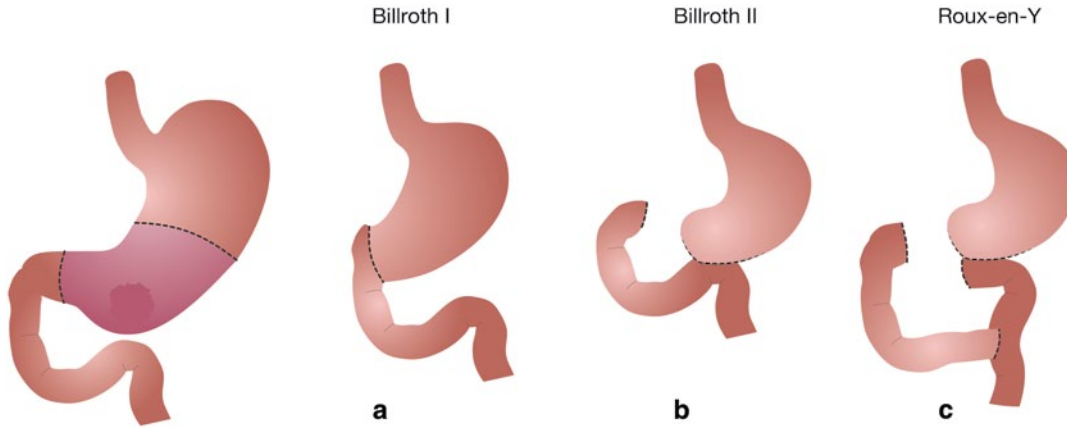

Fig. 12.2 Reconstruction following distal gastrectomy. **a** Schematic drawing of Billroth I reconstruction. **b** Schematic drawing of Billroth II reconstruction. **c** Schematic drawing of Roux-en-Y reconstruction

indicated in most cases of invasive stomach cancer, thus leaving the BI reconstruction an option mainly after resection of benign lesions, noninvasive tumors, or early malignant lesions. It should be noted, that this type of reconstruction, although commonly not used in Western countries, is an often used mode of reconstruction in Asia.

Billroth II

The reconstruction according to Billroth II (BII), first performed in 1885, is characterized by a gastro-jejunostomy of the remaining stomach to the first jejunal loop (Fig. 12.2b) [11]. The advantage of this procedure in comparison to BI is the tension-free anastomosis. The main disadvantage is the un-physiological passage of the bilio-pancreatic juice through the stomach due to the missing pylorus. Some patients develop the so-called afferent loop syndrome (ALS), which is caused by an accumulation of bilio-pancreatic juice in the afferent jejunal segment due to a hampered drainage that leads to pain, nausea, and vomiting.

Roux-en-Y

The Roux-en-Y (RY) reconstruction was first described by Woelfler in 1883 [12] and later popularized by C. Roux from 1893 onwards [13]. The Roux-en-Y reconstruction is characterized (after distal resection) by a gastro-jejunostomy of the remaining stomach to a jejunal limb (mostly the second jejunal loop), which has been excluded from the normal intestinal passage (Fig. 12.2c).

The procedure involves the blind closure of the proximal duodenum and a second anastomosis between the ascended jejunal limb and the first jejunal loop that carries the bilio-pancreatic juice. The main advantage of the procedure is the reduction of bilio-pancreatic reflux into the stomach due to the distance between the stomach and the jejuno-jejunostomy, which normally has a length of at least 40 cm. The main disadvantage is the exclusion of the duodenal segment from the normal intestinal passage. This exclusion might be the reason for the development of the so-called Roux syndrome in up to 10% of patients, characterized by a delayed emptying of the stomach into the efferent jejunal loop in the presence of a nonconstricted gastro-jejunal anastomosis.

Summary of Data from Clinical Trials Comparing Reconstructions After Distal Gastrectomy

A meta-analysis concentrating on the comparison of BI vs. RY for reconstruction after distal gastrectomy for stomach cancer combined three RCTs [14]. In addition, this study also performed a meta-analysis on nine observational clinical studies (OCTs). Not all parameters were available in all RCTs. A significant difference in favor of a RY reconstruction compared to BI could be detected for bile reflux (2 RCTs, 71 vs. 75 patients) and remnant gastritis (2 RCTs, 181 vs. 182 patients), while operation time and hospital stay were significantly longer after RY vs. BI (3 RCTs, 240 vs. 238 patients). Of note, reflux esophagitis showed only a tendency, but was not significantly lower after RY (3 RCTs, 227 vs. 231 patients). This trend is substantiated by a significant reduction of reflux esophagitis after RY vs. BI in the meta-analysis of OCTs (5 OCTs, 322 vs. 397 patients). The anastomotic leak rate and anastomotic stricture rate was equally high in both reconstructions (3 RCTs, 240 vs. 238 patients). Taken together, the meta-analysis demonstrated clinical benefits concerning the reduction of bile acid reflux and its consequences for a RY compared to a BI reconstruction.

A second meta-analysis comparing BI or RY including RCTs of distal gastrectomies of both nonmalignant and malignant patient cohorts is available [15]. This meta-analysis did show no significant difference in total postoperative complications or specifically in the anastomotic leak rate in RY vs. BI (4 RCTs, 185 vs. 189 patients). A significant lower rate of reflux symptoms (5 RCTs, 381 vs. 391 patients), reflux esophagitis (6 RCTs, 340 vs. 372 patients), and gastritis (7 RCTs, 337 vs. 377 patients) was found after RY reconstruction vs. BI, while no difference for dumping syndrome was detected (5 RCTs, 361 vs. 391 patients). No significant difference for operation time was evident (3 RCTs, 106 vs. 114), patients after RY vs. BI had a significantly shorter hospital stay (2 RCTs, 91 vs. 91 patients).

The same publication also reported a meta-analysis comparing RY vs. BII reconstructions. No significant differences in total postoperative complications (2 RCTs, 65 vs. 61 patients), while dumping syndrome (2 RCTs, 83 vs. 78 patients), reflux symptoms (2 RCTs, 83 vs. 78 patients), reflux esophagitis (3 RCTs, 60 vs. 68 patients), and gastritis (6 RCTs, 114 vs. 148 patients) were significantly lower in RY vs. BII reconstructed patients.

A third meta-analysis within the same publication compared BI vs. BII reconstructions. While significantly less overall complications (4 RCTs, 738 vs. 280 patients) as well as specifically less anastomotic leaks (3 RCTs, 708 vs. 248 patients) were found in BI vs. BII reconstructed patients, the mortality rate was not significantly different (3 RCTs, 697 vs. 258 patients). Of note, the local recurrence rate was significantly higher after BI vs. BII reconstruction (2 RCTs, 71 vs. 75 patients). Concerning reflux symptoms (2 RCTs, 66 vs. 39 patients), dumping syndrome (2 RCTs, 66 vs. 39 patients), reflux esophagitis (3 RCTs, 68 vs. 67 patients), and gastritis (5 RCTs, 113 vs. 106 patients) no significant differences were found between BI and BII reconstructions.

Evidence Based Recommendations for the Reconstruction After Distal Gastrectomy

As mentioned above, BI reconstruction is only possible in a minority of cases after distal gastrectomy due to the restricted possibilities to mobilize the duodenum and gastric remnant. Two studies comparing BI vs. BII both reported a higher incidence rate of local recurrence after BI, indicating that resection margins and lymph node dissection might have been chosen too limited in order to perform a tension-free anastomosis. As both BI and BII are associated with similar mortality rates as well as symptoms and consequences of bilio-pancreatic reflux, the BI reconstruction is rarely used for malignant diseases in Western countries.

Both the BI and the BII reconstruction have been shown to be inferior in preventing the symptoms and consequences of bilio-pancreatic reflux when compared to RY reconstruction. As the overall survival of patients depends mainly on a radically performed oncological resection, which is in the case of a planned BII or RY not restricted in its dimension, the decision on one of the two reconstruction techniques should be based on the postoperative complication rate and quality of life. As morbidity rates are similar while symptoms resulting from bilio-pancreatic reflux are significantly higher after BII, a RY reconstruction should be favored.

Reconstruction Following Proximal Gastrectomy

Methods for Reconstruction

Proximal resections (Fig. 12.1b) have seen a revival in recent years due to the high number of early gastric cancers in Asian countries that demand a more limited resection than total gastrectomy due to their low frequency of lymph node metastasis [16]. Reconstruction after proximal gastrectomy was initially performed as a direct esophago-gastrostomy, but this procedure comes along with a high rate of gastric reflux [17]. To prevent the occurrence of gastric reflux, different approaches have been tested, including combining a esophago-gastrostomy with a fundoplication [18], jejunal interposition with and without pouch [19, 20], double tract reconstruction [21], and ileo-colic interposition [22]. To date, only a few nonrecurrent RCTs have been performed, often reporting on few patients only [18–21]. Of note, two RCTs have been published on the topic of including a pouch or not: both favor a pouch when performing a jejunal interposition [19, 20]. With proximal resections becoming the standard operation for early proximal gastric cancers at least in Asia, more RCTs analyzing different reconstruction methods are expected to be conducted within the next years. Currently, no evidence-based advice can be given upon which procedure to favor.

Reconstruction Following Total Gastrectomy

Methods for Reconstruction

Total gastrectomy (Fig. 12.1d) is performed in all cancer patients where a distal or proximal gastrectomy cannot be performed due to oncological radicalness concerning the distance of resection margins towards the tumor, i.e., in adenocarcinomas greater than T2 of the proximal stomach, hereditary (CDH1 mutated) diffuse gastric cancer or signet ring gastric cancer with an insufficient proximal margin. The following reconstructions are most frequently used:

RY is characterized by an esophago-jejunostomy of the remaining esophagus to an ascended jejunal limb and a jejuno-jejunostomy between the ascended jejunum to the first jejunal loop. The reconstruction can be performed with and without a pouch.

Jejunal or colonic interposition: in the first case characterized by an esophago-jejunostomy and a jejuno-duodenostomy of an interposed jejunal segment. The formation of a pouch can be included in the reconstruction. Similarly, a segment of the colon, i.e., the transverse colon or an ileo-cecal segment can be interposed.

Roux-en-Y

The RY reconstruction after total gastrectomy is similar to the RY after distal gastrectomy and has been described first by Orr in 1947 [23]. The technique is similar to the RY after distal gastrectomy and consists of the formation of an esophago-jejunostomy of the remaining esophagus to a jejunal limb, which has been brought up either via the retrocolic (transmesocolic) or antecolic route (Fig. 12.3a). The length of the jejunal segment that has been brought up and thus excluded from the original small intestinal passage is often longer than in the case of RY reconstruction after distal gastrectomy. The esophago-jejunostomy is commonly performed as an end-to-side anastomosis, resulting in a blind ending of the jejunum (jejunal stump), which should be as short as possible.

Jejunal and Colonic Interposition

In order to keep the duodenum in the continuity of the intestinal passage the interposition of a jejunal segment after a partial removal of the stomach has already been used by Roux in 1907 [24]. Longmire was the first to apply this technique after total gastrectomy [25] (Fig. 12.3b). The interposition requires the identification of a long enough jejunal segment (25–30 cm) close to the ligament of Treitz fed by a sufficient jejunal artery. Two anastomoses (a proximal esophago-jejunostomy and a distal jejuno-duodenostomy) re-establish the continuity of the intestinal continuity. Different parts of the colon have also been used to replace the missing stomach [26, 27]. The interposition of a colonic segment is technically more demanding and has not been shown to bring advantages over the jejunal interposition in a randomized trial.

Reconstruction with a Reservoir Formation

In order to re-establish both the intestinal continuity and the physiological function of the stomach to store food, the RY and the jejunal interposition reconstruction have been combined with the formation of a pouch reservoir as a stomach substitute. In addition, also colonic segments have been used for reservoir formations. Multiple different approaches have been described in the literature for the formation of a reservoir, several of them evaluated in RCTs.

Roux-en-y with Pouch

RCT-evaluated reconstructions include the formation of a J-pouch [28, 29], a Ω-pouch [30], a S pouch [31], and an aboral pouch [32]. The formation of a J-pouch involves a side-to side entero-enterostomy of the jejunum and a prolonged jeju-

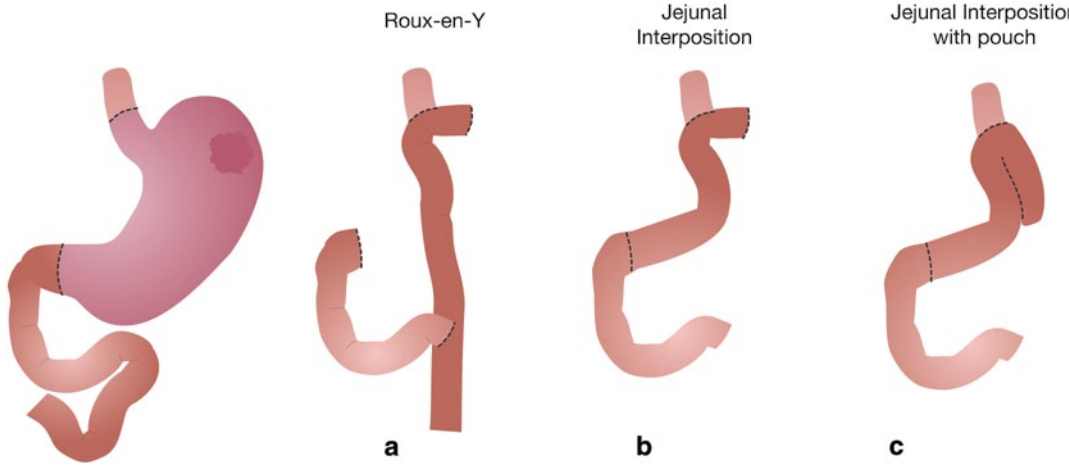

Fig. 12.3 Reconstruction following total gastrectomy. **a** Schematic drawing of Roux-en-Y reconstruction, **b** Schematic drawing of jejunal interposition, **c** Schematic drawing of jejunal interposition with pouch

nal stump all the way to the esophago-jejunostomy with a total length of 15–20 cm (Fig. 12.4a). The Ω-pouch differs from the J-pouch in that the entero-enterostomy is not extended completely to the esophago-jejunostomy (Fig. 12.4b). The S-pouch is formed by accomplishing two entero-enterostomies at the end of the ascended jejunum (Fig. 12.4c). The aboral pouch is formed by fashioning, instead of a simple end-to-side Y-anastomosis of the afferent and efferent jejunal limbs, a long (15 cm) side-to-side antiperistaltic jejuno-jejunostomy (Fig. 12.4d).

Jejunal Interposition with Pouch

Several duodenal passage-preserving reconstruction techniques including the formation of a pouch have been described, the earliest dating back to the 1950s [33, 34]. Only one reconstruction technique, the J-pouch combined with jejunal interpositions has also been evaluated by RCTs (Fig. 12.3c).

Ileo-Cecal Interposition

The idea of using the ileo-cecal valve as a substitute for the cardiac sphincter has first been published by Lee [35] and Hunnicutt [36]. Both authors used an interposition of the terminal ileum and the cecum to bridge the gap after total gastrectomy. This technique is the only one published until today which attempts to include an anatomic barrier between the neo-stomach and the esophagus to prevent bilio-pancreatic reflux. In addition, the colonic segment by nature functions as a kind of reservoir due to its larger diameter when compared to a simple jejunal interposition. No data from randomized controlled studies in humans is available. Nonetheless, data from mini-pigs after distal resection [37] and prospective and retrospective studies on patients after total gastrectomy [22, 38] indicate a good functioning of the ileo-cecal valve as an antireflux barrier. Nevertheless, the technically demanding and thus morbidity-prone operation has not been evaluated in RCTs.

Summary of Data from Clinical Trials Comparing Reconstructions After Total Gastrectomy

Reconstruction With or Without a Reservoir

A meta-analysis identified 13 RCTs (search until October 2008) addressing this question [39]. Nine RCTs compared Roux-en-Y reconstruction with (PRY) and without pouch (RY). Not all trials reported on all analyzed parameters. Seven RCTs could be combined for the analysis of morbidity or mortality. No significant difference could be shown for PRY vs. RY (187 vs. 200 patients). Operation time (3 RCTs, 58 vs. 44 patients) and

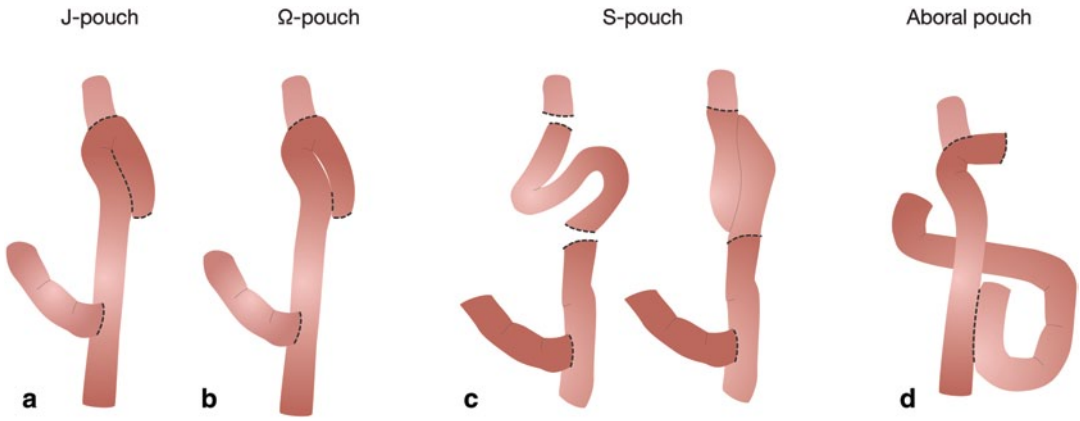

Fig. 12.4 Roux-en-Y reconstruction with a reservoir formation. **a** Schematic drawing of a J-pouch, **b** Schematic drawing of a Ω-pouch, **c** Schematic drawing of a S-pouch, **d** Schematic drawing of an aboral-pouch

hospital stay (two RCTs, 34 vs. 32 patients) did not increase significantly in PRY vs. RY. Dumping syndrome was significantly lower in PRY vs. RY 6 months (2 RCTs, 33 vs. 29 patients) and 12 months postsurgery (4 RCTs, 58 vs. 51 patients). Reflux was significantly lower in patients after PRY vs. RY 12–15 months postsurgery (2 RCTs, 19 vs. 18 patients). A tendency towards better food intake (measured as > or < than 50 % of preoperative value) for PRY was observed at 3 and 6 months, while food intake was significantly better in PRY vs. RY at 12–15 months postsurgery (3 RCTs, 42 vs. 32 patients). Concerning the quality of life two RCTs used the same score and could be combined. No difference was detected when all patients were analyzed at 6, 12, and 24 months (2 RCTs, 72/52/35 vs. 66/46/33 patients). Nevertheless, both studies independently described significant differences in favor of a pouch at 24 and 30–60 months. If only patients with R0 resection in one trial and 5-year survival of the other trial were combined, a significantly better quality of life was achieved in RYP vs. RY at 12 and 24 months (2 RCTs, 33/22 vs. 29/22 patients).

Four RCTs compared jejunal interposition with (JPI) and without (JI) pouch. Due to heterogenously reported parameters a meta-analysis could only be performed for mortality, which showed no significant difference between JPI vs. JI (3 RCTs, 67 vs. 46 patients).

Preservation of the Duodenal Passage

Nine RCTs compared duodenal preserving reconstructions (DP) by jejunum interposition with and without pouch to nonduodenal preserving (NDP) Roux-en-Y reconstruction with and without pouch. These studies have been jointly analyzed in a meta-analysis (search until May 2012) [40]. Four RCTs could be analyzed for morbidity differences between DP and NDP (148 vs. 153 patients), and 5 RCTs could be analyzed for mortality differences (169 vs. 176 patients), resulting in no statistical difference between the 2 procedures. Operation time was significantly longer in DP vs. NDP (6 RCTs, 207 vs. 222 patients). Body weight could be analyzed in 2 studies (DP 83 vs. NDP 84 patients) at 3 and 6 months, showing a statistically significant increased weight in DP. Four studies statistically described body weight development at different later time points, precluding a formal meta-analysis. Nevertheless, each study reported no statistical difference at time points >12 months postsurgery. Bilio-pancreatic reflux was analyzed in 2 and for 1 time point in 3 RCTs, showing no difference between DP and NDP at 3, 6, 12 and 24 months (20/20/30/19 vs. 22/22/32/21 patients). The incidence of dumping syndrome was significantly lower in DP vs. NDP at 3, 6, and 24 months (3 RCTs, 95/95/95 vs. 102/102/101 patients), but not at 12 months with the inclusion of one more trial (4 RCTs, 105 vs. 112 patients). Of note, when only RCTs which included a pouch were analyzed, no statistical difference between DP vs. NDP could be detected (2 RCTs for 3, 6, 24 months with 20/20/19 vs. 30/30/28 patients and 3 RCTs for 12 months with 30 vs. 50 patients). Quality of life could not be analyzed in a combined fashion due to different measurement scales. Of 5 RCTs, only 1 study showed an improved quality of life at 6 months in DP vs. NDP (24 vs. 24 patients), while all others reported no statistical difference at this, earlier, and later time points (up to 60 months).

Evidence-Based Recommendations for the Reconstruction After Total Gastrectomy

Two important questions concerning the reconstruction after gastrectomy have been addressed by meta-analyses, combining each several RCTs. Concerning the construction of a pouch, the pooled data clearly shows a clinical benefit for patients receiving a pouch together with a RY reconstruction, at least for the first postoperative year. Reflux, as well as dumping syndrome, eating capability, and quality of life are significantly better with than without pouch, while morbidity and mortality rates are similar. Data on pouch reconstruction after jejunal interposition document no increased mortality when a pouch is included, but data on postgastrectomy syndromes and quality of life are not strong enough to draw decisive

conclusions yet. Concerning the preservation of the duodenal passage, construction of a jejunal interposition with and without a pouch is not associated with a higher mortality or morbidity rate compared to RY, while operation time is significantly longer. Postgastrectomy syndromes in pouch reconstructed patients as well as quality of life did not show a benefit for jejunal interposition. Both procedures can thus be performed on par based on current knowledge.

Final Conclusion

For this chapter, the authors have tried to provide the reader with a summary of the available data on reconstruction techniques after major gastric surgery. Only data from RCTs and when possible from meta-analyses are presented. On a cautionary note: a meta-analysis can only be as good as the single RCTs included. The presented meta-analyses use stringent selection criteria on individual trials before inclusion. This, nevertheless, often results in comparisons with a restricted number of trials with low numbers of patients. This has to be kept in mind, as not finding a significant difference might be a result of the low patient numbers. Of course, notwithstanding the merits of evidence-based medicine, the individual patient has to be taken into account, balancing factors such as the preoperative state and life expectancy with the complexity and associated morbidity rate of the different reconstruction techniques.

Based on the available data the authors advocate for distal gastric resection a Roux-en-Y reconstruction. For proximal reconstruction available data do not support an evidence-based suggestion yet. For total gastrectomies equal results are obtained by either a Roux-en-Y reconstruction with a J- or Ω-pouch or a jejunal interposition with pouch.

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Lymphadenectomy—D1, D2, and D3

13

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Introduction

Adequate local control is essential for the treatment of gastric cancer. When Theodor Billroth performed the first successful gastrectomy in 1881, he also removed some enlarged nodes. Since then, major improvements have been made in the surgical treatment of gastric cancer. Postoperative mortality has dropped from nearly a 100% in the early days to below 1% in experienced centers nowadays, while survival has strongly improved over the years. One of the main reasons for this improvement in survival is standardization of the surgical approach including a standardized dissection of lymph nodes surrounding the stomach. The systematic dissection of gastric lymph nodes is a highly effective procedure to treat lymph node metastases in gastric cancer. This standardized lymph node dissection was established by the Japanese Research Society for the study of Gastric Cancer.

Over the past 30 years, the extent of lymphadenectomy has been subject of a worldwide debate. Many trials have been performed in which the extent of lymph node dissection was studied. The standardized lymph node dissection was developed in Japan, and in Asian countries an extended lymphadenectomy, including lymph nodes around the celiac axis, has been a standard procedure for decades. For many years in Western countries a more limited lymph node dissection, only involving nodes directly adjacent to the stomach, was standard of care. Recent updates of European and the USA guidelines have incorporated an extended lymph node dissection as well [1, 2].

The current chapter covers the anatomy of lymph node stations surrounding the stomach, the explanation of different types of lymph node dissection, studies on lymphadenectomy and their effect on daily clinical practice, and the use of predictive and prognostic models on lymph nodes in gastric cancer. Furthermore, as the debate on the type of lymph node dissection to a great extent is a debate on surgical quality assurance, this subject will also be discussed in this chapter.

Anatomy

Since 1963, the Japanese Research Society for Gastric Cancer (JRSGC) has published several editions of the General Rules for Gastric Cancer Study. In this classification, a detailed description of possible surgical and pathological findings is described. The first English edition of this classification, which was based on the 12th Japanese edition, was published in book form [3], while the second English edition was published as a journal article [4]. Several studies on lymph drainage pathways have made it possible

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to clearly distinguish different locations of lymph nodes around the stomach. From these studies, it became clear that metastasis can directly "jump" to higher group numbers, rather than starting at the nodes closest to the stomach followed by further spreading.

The locations are numbered from 1 to 16 (Fig. 13.1). Anatomical borders of all lymph node stations are shown in Table 13.1.

Regional lymph nodes are further classified into four groups, based on the location of the primary tumor. Nodes closest to the tumor are classified as N1, followed by N2 nodes further away from the primary tumor, followed by N3 and N4. The N type of lymph node station also depends on the primary location of the tumor, which is specified in Table 13.2.

The type of lymphadenectomy depends on the lymph node stations that are removed. In a limited D1 dissection, the stomach with the primary tumor and perigastric (N1) lymph nodes are removed. For a D2 lymphadenectomy, the nodes along the left gastric, the common hepatic, the splenic, and the left hepatoduodenal artery are also removed, as well as some stations that differ for proximal, middle, and distal tumors (N2 nodes). In previous versions, it was recommended to perform a distal pancreaticosplenectomy with every D2 dissection. This has been abandoned and is now only advised for tumors with invasion of the greater curvature. With a D4 dissection, the N1 and N2 nodes are removed with the para-aortic nodes.

Randomized Controlled Trials on the Extent of Lymph Node Dissection

The key point of the debate on the extent of lymphadenectomy for gastric cancer has always been the balance between maximum locoregional control and acceptable morbidity and mortality. In Japan, an extended D2 lymph node dissection has been the standard of care for decades and is generally performed by experienced surgeons in specialized centers. Western surgeons have lower annual caseloads (except for a few high-volume centers) and mostly performed a more limited D1 dissection because of the higher morbidity and mortality associated with extended lymphadenectomy performed in low volumes. As Japanese long-term survival results were impressively better compared with those of the West [6], several groups decided to perform trials comparing a D1 with D2 lymphadenectomy. A summary of all described trials is given in Table 13.3.

South Africa

Dent et al. performed the first study between 1982 and 1987 in South Africa. In this randomized trial, 403 patients were evaluated for surgery. The majority of patients were ineligible due to advanced disease, and 43 patients were randomized between a D1 resection and a D2 resection. Although there was no in-hospital mortality, patients in the D2 group had a significantly longer operating time, a greater blood transfusion requirement, and had a longer hospital stay. With a median follow-up of 3.1 years, no differences in survival were detected between the two study arms. The authors concluded that a D2 lymphadenectomy should not be performed in daily clinical practice [7].

Hong Kong

The second randomized study on this subject was performed in Hong Kong, and was published in 1994 [8]. Between 1987 and 1991, 55 patients with antral gastric cancer were randomized for a limited or an extended lymphadenectomy. An extended lymphadenectomy consisted of a total excision of the greater and lesser omenta, splenectomy, distal pancreatectomy, lymphatic clearance of the celiac axis and its trifurcation, and skeletonization of the vessels in the porta hepatis. A total of eight surgeons performed all procedures, while three of the surgeons performed 75% of the procedures. Although all surgeons involved in the trial were trained initially and supervised in the procedures, training methods were not described. Pathology specimens were processed in a standard manner.

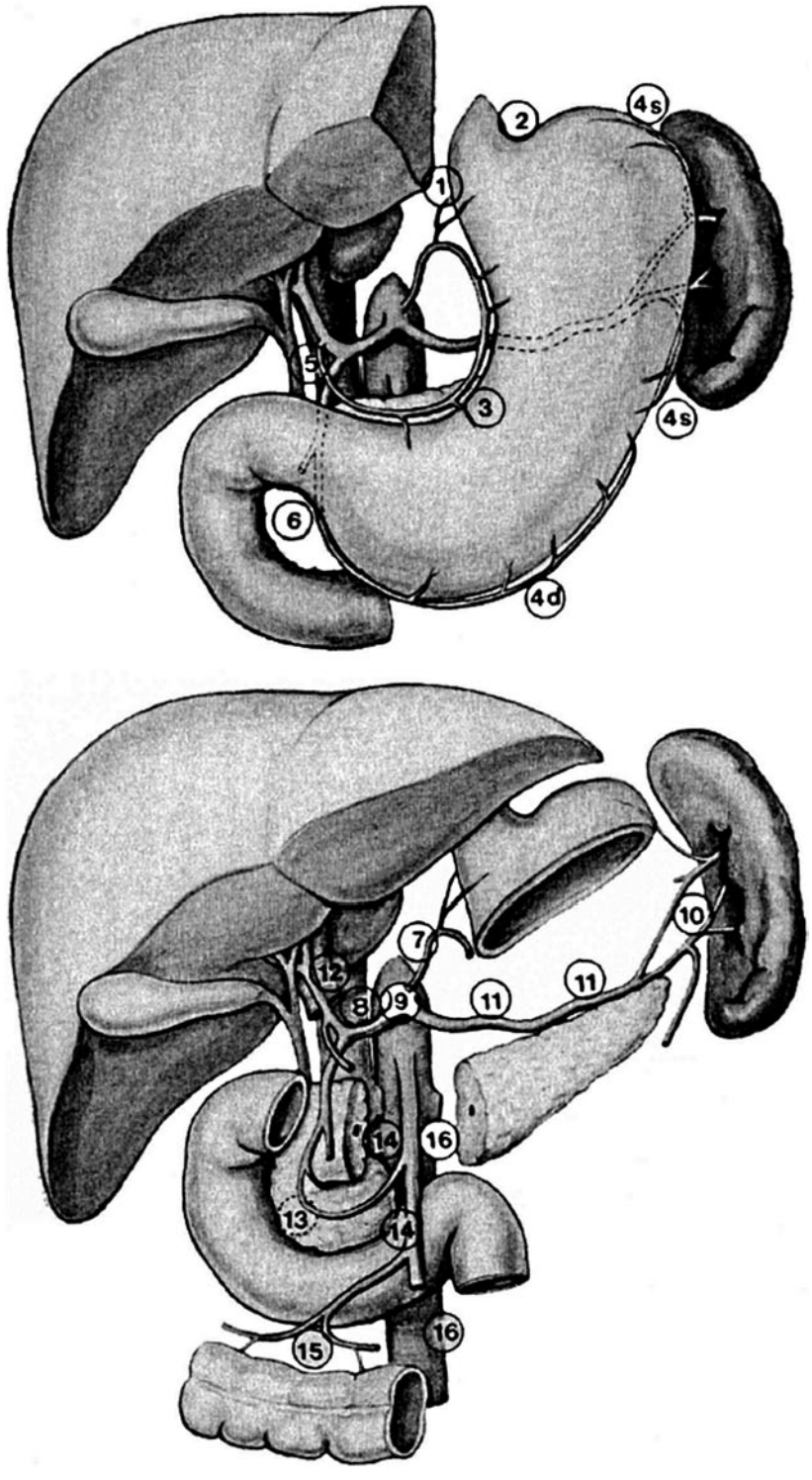

Fig. 13.1 Lymph node stations as described by the JRSGC

Table 13.1 Lymph node stations and their anatomical borders [5]

Station	Description	Anatomical border
1	Right cardiac	Perigastric nodes on the right side of the cardia. Nodes along the cardio-esophageal branch of the left gastric artery, from its origin to the esophageal hiatus
2	Left cardiac	Perigastric nodes on the left side of the cardia
3	Lesser curvature	Nodes along the inferior branch of the left gastric artery and along the right gastric artery distal to the first gastric branch
4	Greater curvature	This location is divided into a left (s) and a right (d) part defined by the water shed. The left part is divided into a proximal (sa) and a distal part (sb). 4sa is located around the short gastric arteries and 4sb are the nodes along the left gastroepiploic artery. 4d is located along the right gastroepiploic artery distal to the first gastric branch
5	Suprapyloric	Nodes at the origin of the right gastric artery including the first gastric branch
6	Infrapyloric	Perigastric nodes on the greater curvature of the pylorus. Nodes along the gastroepiploic vessels from their origin to their first gastric branches. The origin of the vein is situated just after the gastrocolic trunk
7	Root left gastric artery	Nodes on the left gastric artery from its origin to the bifurcation into the cardioesophageal and lower branch
8	Common hepatic artery	Nodes around the common hepatic artery from the celiac trunk to the branching off of the gastroduodenal artery
9	Celiac axis	All nodes on the celiac axis including the origins of the common hepatic and splenic artery
10	Splenic hilum	All nodes at the splenic hilus, distal to the pancreas tip. At the lower pole, the first gastric branch of the left gastroepiploic artery defines the border between 10 and 4sb
11	Splenic artery	Nodes along the splenic vessels up to the distal end of the pancreas tail. These nodes are divided into proximal (p) and distal (d) nodes
12	Hepatoduodenal ligament	Group number 12 is divided up in three parts: 1. left side of the hepatic artery (12a), 2. right side of the ligament and posterior to the choledochal duct (12b) and 3, just posteriorly to the portal vein (12p)
13	Retropancreatic	Nodes along the superior and inferior posterior pancreaticoduodenal arteries on the posterior side of the pancreas. The portal vein marks the lateral left border of this location. The upper border of location 13 coincides with 12b and 12p
14	Root of mesentery	Nodes along the superior mesenteric vessels. The lateral border is confined by the bifurcation of the gastrocolic trunk, the lower border by the branching off of the jejunal veins and the upper border is typified by the origin of the superior mesenteric artery
15	Middle colic vein	Nodes in the transverse mesocolon
16	Para-aortic	Nodes around the abdominal aorta and inferior caval vein. Right and left border are defined as the hili of the left and right kidney

There was only one case of postoperative death in the extended lymphadenectomy group. Operating time was longer in the extended group (median 260 versus 140 min), and had more operative blood loss (600 versus 300 ml). The complication rate was higher in the extended lymphadenectomy group with seven versus no patients needing a relaparotomy because of a left subphrenic abscess. Median survival was significantly higher in the limited lymphadenectomy group (1511 versus 922 days). The high rate of subphrenic abscess in the extended lymphadenectomy group is explained by the pancreatic tail resection. The authors conclude that their study does not support routine use of an extended lymphadenectomy for gastric cancer.

Table 13.2 Lymph node groups by tumor location [4]

Lymph node station	Location	LMU/MUL MLU/UML	LD/L	LM/M/ML	MU/UM	U	E+
No. 1	Rt paracardial	1	2	1	1	1	
No. 2	Lt paracardial	1	M	3	1	1	
No. 3	Lesser curvature	1	1	1	1	1	
No. 4sa	Short gastric	1	M	3	1	1	
No. 4sb	Lt gastroepiploic	1	3	1	1	1	
No. 4d	Rt gastroepiploic	1	1	1	1	2	
No. 5	Suprapyloric	1	1	1	1	3	
No. 6	Infrapyloric	1	1	1	1	3	
No. 7	Lt gastric artery	2	2	2	2	2	
No. 8a	Ant comm hepatic	2	2	2	2	2	
No. 8b	Post comm hepatic	3	3	3	3	3	
No. 9	Celiac artery	2	2	2	2	2	
No. 10	Splenic hilum	2	M	3	2	2	
No. 11p	Proximal splenic	2	2	2	2	2	
No. 11d	Distal splenic	2	M	3	2	2	
No. 12a	Lt hepatoduodenal	2	2	2	2	3	
No. 12b,p	Post hepatoduod	3	3	3	3	3	
No. 13	Retropancreatic	3	3	3	M	M	
No. 14v	Sup mesenteric v.	2	2	3	3	M	
No. 14a	Sup mesenteric a.	M	M	M	M	M	
No. 15	Middle colic	M	M	M	M	M	
No. 16a1	Aortic hiatus	M	M	M	M	M	
No. 16a2,b1	Para-aortic, middle	3	3	3	3	3	
No. 16b2	Para-aortic, caudal	M	M	M	M	M	
No. 17	Ant pancreatic	M	M	M	M	M	
No. 18	Inf pancreatic	M	M	M	M	M	
No. 19	Infradiaphragmatic	3	M	M	3	3	2
No. 20	Esophageal hiatus	3	M	M	3	3	1
No. 110	Lower paraesophag	M	M	M	M	M	3
No. 111	Supradiaphragmatic	M	M	M	M	M	3
No. 112	Post mediastinal	M	M	M	M	M	3

U upper 1/3, *M* middle 1/3, *L* lower 1/3

Table 13.3 Randomized studies on the extent of lymph node dissection in gastric cancer

Trial	Country	N	Comparison	Morbidity	Mortality	Overall survival
Dent [7]	South Africa	43	D1 versus D2	–	0 versus 0 %	At 3.1 years: 82 versus 77 % not significant
Robertson [8]	Hong Kong	55	D1 versus D2	0 versus 23 % relaparotomies	0 versus 3 %	At 4.1 years: 46 versus 38 % $P=0.04$
Cuschieri [9, 10]	UK	400	D1 versus D2	28 versus 46 % $P<0.001$	6.5 versus 13 % $P=0.04$	At 5 years: 35 versus 33 % not significant
Bonenkamp [11, 13, 14]	Netherlands	711	D1 versus D2	25 versus 43 % $P<0.001$	4 versus 10 % $P=0.004$	At 15 years: 21 versus 29 % $P=0.34$ Gastric cancer specific survival 48 versus 37 % $P=0.01$
Wu [16]	Taiwan	221	D1 versus D3	7.3 versus 17.1 %	0 versus 0 %	At 5 years: 53.6 versus 59.5 % $P=0.041$
Sano [1818, 19]	Japan	523	D2 versus D2+ para-aortic	20.9 versus 28.1 % $P=0.067$	0.8 versus 0.8 %	At 5 years: 69.2 versus 70.3 % $P=0.85$
Degiuli[20, 21]	Italy	267	D1 versus D2[a]	12.0 versus 17.9 % $P=0.178$	3.0 versus 2.2 % $P=0.722$	At 5 years: 66.5 versus 64.2 % $P=0.695$

[a] D2 without routine distal pancreaticosplenectomy

UK Medical Research Council Trial

One of the five large trials on this subject was performed in the United Kingdom [9, 10]. In this trial that was performed between 1986 and 1993, 737 patients with histologically proven adenocarcinoma of the stomach were registered and underwent a staging laparotomy. Of these patients, 400 patients were eligible for the study (defined as stage I–III gastric cancer without positive infracolic para-aortic nodes) and were peroperatively randomized for gastrectomy with a D1 or D2 dissection, whereas a D2 dissection was routinely combined with distal pancreatectomy and splenectomy. All surgeons were trained with an operative booklet and videotape on the procedure, but surgeons were not supervised during the procedure.

A median of 13 nodes were removed in the D1 group, and 17 in the D2 group. Operative morbidity was 28 % in the D1 group and 46 % in the D2 group. Postoperative in-hospital mortality was higher in the D2 group (13 versus 6.5 %). Distal pancreaticosplenectomy had a significant adverse effect on both morbidity and mortality. When adjusting the analysis for distal pancreaticosplenectomy, the difference in mortality and morbidity between the two groups became non-significant. No differences in overall survival, as well as disease-specific survival, were detected between the two groups. The authors conclude that a D2 lymphadenectomy including distal pancreaticosplenectomy offers no survival advantage over a D1 lymphadenectomy, but no conclusions can be drawn on an extended lymphadenectomy without pancreatic tail or splenectomy.

Dutch Gastric Cancer Trial

At the same time, a large Dutch trial was open for accrual [11]. Between 1989 and 1993, 1078 patients were randomized between a D1 and D2 lymph node dissection. Randomization was performed before surgery to arrange adequate supervision during surgery. During the first 6 months of the trial, participating surgeons were instructed by a Japanese gastric cancer surgeon. After this period, one of eight specially trained surgeons attended every D2 dissection, while the study coordinator attended all D1 operations. Besides an instruction book and videotape, regular meetings were held for all participating surgeons. Quality control was carried out by relating the number and location of lymph nodes detected at pathological examination to the guidelines of

the study protocol. If at pathological examination lymph nodes were detected other than specified by the protocol, this was called "contamination." If a pathologist could not detect lymph nodes in stations that should have been dissected, this was called "noncompliance." This was monitored during the study, and feedback was given to the surgeons, as both contamination (mainly with a D1 dissection) and noncompliance (mainly with a D2 dissection) could blur the study results. During the study, a routine distal pancreatectomy and splenectomy were performed with a D2 lymphadenectomy for proximal tumors.

The main reason for exclusion of patients was unavailability of a trained surgeon at the operation ($N=35$). For 285 patients who underwent a laparotomy, a curative resection was not possible. Of the 1078 randomized patients, 711 patients underwent a curative resection.

The mean number of investigated lymph nodes was higher in the D2 group (31.5 versus 18.4). Hospital mortality was higher after a D2 compared to a D1 dissection (10 versus 4%). Morbidity was also higher in the D2 group (43 versus 25%). At 5 years, no differences in overall survival (34 versus 33%) or recurrence (42% D1 versus 37% D2) were detected [12]. Furthermore, patients who underwent a distal pancreatectomy or splenectomy had a lower overall survival rate. Based on these results, in 1999 the authors concluded that a D2 lymphadenectomy should not be advised.

After a median follow-up of 11 years, survival rates in both groups were reassessed [13]. Overall survival was 30% for the D1 group, and 35% for the D2 group. Subgroup analysis revealed that a D2 dissection was associated with better survival in patients with N2 disease. It was concluded that a D2 dissection might be beneficial for patients with N2 disease, but these patients are difficult to identify preoperatively.

In 2010, a new report on this study was published, now with a median follow-up of 15 years [14]. With this analysis, 173 patients (24%) were alive without recurrence (D1 82 patients, D2 91 patients), and one patient was alive with recurrence in the D2 group. In total, 217 patients died without recurrence, and 320 patients died with recurrence (188 D1 group, 131 D2 group). Fifteen-year overall survival in the curative resection group was 21% for the D1 group and 29% for the D2 group, but this difference was not significant. When analyzing cause of death, gastric-cancer-related death was significantly higher in the D1 group compared with the D2 group (Hazard ratio 0.74 for D1 versus D2). Based on these new results, the authors conclude that when it is possible to avoid postoperative mortality, a D2 lymphadenectomy without routine distal pancreaticosplenectomy should be the recommended therapy.

Cochrane Review

In 2003, a Cochrane review was published that was based on these first four randomized studies [15]. With an increased mortality for the extended lymphadenectomy group, no survival benefit for an extended lymph node dissection was found. However, subgroup analysis revealed that in pT3+ tumors an extended lymphadenectomy was associated with improved survival. The authors conclude that further studies on the extent of lymphadenectomy should be performed only with experienced surgeons, eliminating contamination and noncompliance.

Taiwan

When results of the Dutch and MRC trials became available, it was suggested that a trial performed at a single high-volume center might show a benefit for a D2 dissection as postoperative mortality is generally low in experienced centers. Therefore, a randomized trial was set up to compare a limited with an extended lymphadenectomy in one hospital in Taiwan [16]. Between 1993 and 1999, 335 patients were registered, of which 221 patients were randomized between a D1 and D3 lymphadenectomy. All procedures were performed by three surgeons, one of which was trained in Japan, while the other two surgeons were then trained by the first surgeon. Pa-

thology specimens were processed in a standardized manner.

Morbidity was higher in the D3 group (17.1 versus 7.3%) and a D3 lymphadenectomy was associated with longer operating time and greater blood loss. No postoperative deaths were reported. Five-year overall survival was significantly higher in the D3 group (59.5 versus 53.6%). Disease specific survival was also significantly higher in the D3 group. The authors conclude that an extended lymphadenectomy is the treatment of choice, and that this should be performed by well trained and experienced surgeons [17].

Japanese Study

While in Western countries, a D2 lymphadenectomy is called "extended," Japanese surgeons perform a D2 dissection routinely, and reserve the term "extended" for para-aortic node dissection. Lymph node metastases generally spread from the perigastric nodes to the nodes around the celiac axis. The last stations of lymph drainage before entering the systemic circulation are the para-aortic nodes. Therefore, removing these nodes can be considered the final step of preventing lymph node disease to become systemic disease. However, para-aortic node dissection requires advanced operating technique and comes with increased risk of postoperative morbidity.

In a Japanese study the effect of a D2 lymphadenectomy with or without para-aortic node dissection was investigated [18, 19]. Between 1995 and 2001, 523 patients from 24 hospitals were randomized intraoperatively between D2 versus D2 plus para-aortic node dissection. Only surgeons who had performed at least 100 D2 gastrectomies or institutions with an annual caseload of 80 or more were selected for the study. During the study, videos of the para-aortic dissection were discussed with participating surgeons. Pancreatectomy was performed only in patients with pancreas involvement of the tumor (11%), while splenectomy was performed in most cases.

Median operation time was 63 min longer in the para-aortic group, and peroperative blood loss was increased in the para-aortic group. Morbidity was significantly higher in the para-aortic group (28.1 versus 20.9%). In both groups there were two cases of in-hospital mortality (0.8%). No differences in overall survival or recurrence-free survival were detected, but in both groups, overall survival was high when compared to Western studies (69.2 and 70.3%). In multivariate analysis, again no differences in overall survival were detected. Based on these results, the authors conclude that a D2 lymphadenectomy with para-aortic node dissection should not be recommended, and that D2 dissection alone should be performed in hospitals with sufficient experience.

Italian Gastric Cancer Study Group

To find a benefit of an extended lymph node dissection for Western patients, the Italian Gastric Cancer Study Group recently performed a study comparing D1 with D2 lymph node dissection only with surgeons experienced in D2 dissections [20]. Between 1998 and 2006, 617 patients were registered in five specialized centers, and 267 patients were randomized for D1 or D2 lymphadenectomy. Splenopancreatectomy was not considered as a routine part of surgery. The spleen was only removed with the tumor close to the spleen. The pancreatic tail was only removed with pancreatic involvement. Pathology specimens were processed in a standardized manner. Only experienced surgeons participated in the trial, although the caseload per surgeon was not reported.

The mean number of nodes removed in the D1 group was 28.2, and the mean number of nodes removed in the D2 group was 37.3. Contamination and noncompliance were registered and contamination occurred in 17.3% of the D1 patients, while noncompliance occurred in 33.6% of the patients who underwent a D2 dissection. Although morbidity was higher in the D2 group (17.9 versus 12.0%), this did not reach significance. No significant difference was found in postoperative mortality as well. After a median follow-up of 8.8 years, no significant difference in overall survival was detected between the two groups. However, in a subgroup of pT2-4 and N+ patients, D2 lymphadenectomy was associated

with better survival compared with a D1 lymphadenectomy [21].

In the discussion, the authors state that accrual went slow due to reluctance of several surgeons to include patients in a trial with an "inferior" D1 arm. The trial therefore was closed just before the accrual target was met. The authors conclude that in patients with advanced disease and positive lymph nodes, a D2 lymphadenectomy may be a better choice.

Nonrandomized Studies

Besides the few randomized studies on this subject, a multitude of nonrandomized comparisons and case series of limited and extended lymphadenectomy have been published. A large number of these, often single-institution, series show a low-postoperative mortality after an extended lymphadenectomy. This reflects the difference between large centers with high caseloads being able to perform with low-operative mortality, while in nationwide trials which more reflect general practice, postoperative mortality is often higher.

Conclusions

In conclusion, there has been an extensive debate on the role of a D2 lymph node dissection. Based on more recent results, an extended lymphadenectomy is now also in the West considered a recommended type of surgery for advanced gastric cancer. This has been integrated into clinical practice guidelines both from Europe and the USA [1, 2]. More extended lymph node dissections (D4) are currently not recommended.

Spleen and Distal Pancreas Resection

The focus of the lymphadenectomy studies has always been on which nodes to resect or not. However, subgroup analyses of several of the randomized studies have shown that splenectomy and pancreatectomy might very well explain morbidity and mortality associated with a D2 dissection to a great extent. In the rules of the Japanese Research Society on Gastric Cancer that were used in during the MRC and Dutch trial, routine removal of station number 10 (splenic hilus), which is not possible without splenectomy, was mandatory for all tumors in the upper part of the stomach. This has later been changed to tumors with invasion of the greater curvature [22].

The adverse effect of splenectomy combined with a D2 distal gastrectomy can be explained by the possibility of ischemia of the remnant stomach, as the left gastric artery is divided at its origin, and the short gastric arteries are the only blood supply to the stump. After D1 distal gastrectomy, this is less of a problem as the left gastric artery is divided more peripherally. An option might be to consider total gastrectomy when splenectomy cannot be avoided [23]. Another explanation of the adverse effect of splenectomy might be the function of the spleen in the immune system. The adverse effect of distal pancreatectomy might be the subclinical leakage of pancreatic juice in close proximity of the proximal anastomosis.

In the MRC trial, distal pancreaticosplenectomy had a significant adverse effect on morbidity and mortality [9]. In this trial, 56% of patients in the D2 group underwent both a pancreatectomy and splenectomy, while 35% did not have splenectomy or pancreatectomy. In the D1 group, this was 4% (both removed) and 69% (none removed), while 27% had splenectomy only. In the D1 group, splenectomy was only performed in case of a proximal tumor where the surgeon considered splenectomy to be necessary. Distal pancreatectomy in this group was only performed in case of direct tumor ingrowth. In multivariate analysis, after adjustment for pancreaticosplenectomy, the difference in morbidity and mortality between the D1 and D2 group became nonsignificant. When comparing overall survival between the three groups, the pancreaticosplenectomy group had the poorest survival, followed by the splenectomy-only group, followed by the group where both organs were left in situ. When comparing the D1 and D2 groups where the spleen and pancreas were not removed,

overall survival was higher in the D2 group. The authors however, were cautious to draw conclusions based on this observation, as it was only a subgroup analysis.

In the Dutch Gastric Cancer Group study, a separate report on risk factors of adverse outcomes was published [23]. Of the 711 patients that were eligible, 58 underwent splenectomy only, and 107 underwent distal pancreaticosplenectomy. On univariate analysis, both splenectomy and pancreatectomy were associated with increased postoperative mortality and morbidity. On multivariate analysis, both remained significant risk factors for surgical and overall complications, whereas splenectomy remained a significant risk factor for hospital death (relative risk 2.16). The effect of splenectomy on hospital death was greater than the effect of lymphadenectomy. When looking at overall survival in the Dutch study, 11-year survival was very poor in the group of patients with lymph node metastases in station number 10 (11%) and 11 (8%), suggesting that the relevance of resecting these nodes might be questioned [13]. Based on this study, the authors conclude that a D2 lymphadenectomy without distal pancreaticosplenectomy might be the treatment of choice [24].

In several smaller randomized studies the effect of pancreatectomy and/or splenectomy on survival has been investigated. In a Japanese study, 110 patients were randomized for either gastrectomy with pancreatic tail resection, or gastrectomy without pancreatic tail resection but with spleen resection. Although morbidity was slightly higher in the group with pancreatic tail resection, no differences in overall survival were detected [25].

In a Chilean trial, 187 patients were randomized between a D2 total gastrectomy with or without splenectomy. Morbidity was significantly higher in the splenectomy group, but no differences in postoperative mortality or overall survival were detected. Based on this study, the authors conclude that a D2 lymphadenectomy should not necessarily be combined with splenectomy [26].

The largest trial published so far is a Korean trial, in which 207 patients were randomized between total gastrectomy with D2 lymphadenectomy with or without splenectomy. Surgical morbidity was higher in the splenectomy group (15.4 versus 8.7%), and overall survival was also higher in the splenectomy group (54.8 versus 48.8%) but this did not reach statistical significance [27].

In a recent meta-analysis, data of the abovementioned trials on this subject were combined. No significant differences in mortality or overall survival were detected between spleen preservation versus spleen resection [28]. However, no data from the large lymphadenectomy trials (MRC and DGCT) were included in this meta-analysis.

The results of the Japanese JCOG 0110 study on this subject are awaited with great interest [29].

Overall, it can be concluded that there is evidence in large randomized studies that pancreas and spleen preservation is associated with lower postoperative mortality, and should only be advised with direct ingrowth of the tumor in these organs.

Maruyama Index

To better predict lymph node involvement in resectable gastric cancer, the Maruyama computer program was developed. This program contains data of 3843 patients who underwent D2 gastric cancer surgery in the National Cancer Center hospital in Tokyo. By entering several patient and tumor variables, the data of a given case are matched with patients in the database, and the likelihood of lymph node metastases for each of the 16 stations are predicted. The Maruyama computer program is intended for use in the operating theatre to identify nodal stations highly at risk.

The sum of the percentages of lymph node stations 1–12 that have not been resected has later been called the Maruyama Index (MI) of unresected disease [30]. The MI has been used to predict survival in patients with detailed information on the removed lymph node stations [30, 31]. Due to its complexity, the MI is not frequently used in Western countries.

Surgical Quality Assurance in Gastric Cancer

The high-postoperative mortality rates that are reported in the Western lymphadenectomy trials are often explained by the low hospital volumes and relatively low surgeon experience with extended lymph node dissection in Western countries. In general, Japanese surgeons have a much higher exposure to gastric cancer than their Western colleagues, except some Western surgeons working in high-volume dedicated centers.

Some of the described randomized trials had quality assurance programs for participating surgeons. However, most patients with gastric cancer are treated outside the framework of randomized studies. For these patients, quality improvement on a nationwide level is necessary. Several countries and regions have started local and national quality assurance programs for different types of cancer, including gastric cancer. The most frequently quality assurance tools are referral of patients to high-volume centers and closing low-volume centers, and clinical auditing.

The first study on the effect of annual hospital volume and outcomes was published in 1979 [32]. Another landmark study on this subject was published in 2002 [33]. In this study with data on approximately 2.5 million surgical procedures in the USA, for several surgical procedures it was shown that high hospital volume is associated with decreased postoperative mortality. Since then, many groups have investigated the effect of hospital volume on outcomes in gastric cancer, and in the majority of these studies, increasing hospital volume is associated with improving outcomes [33–48]. However, the definition of high volume differs between the published studies.

In 2003, the available evidence on hospital volume in gastric cancer has led to national centralization of gastric cancer surgery in several countries. For instance, before 2003, 37 hospitals in Denmark performed gastrectomies, and after 2003 only 5 (university) hospitals were allowed to perform these operations. This has led to a decrease in postoperative mortality from 8.2 to 2.4 %, and a significant increase in the number of resected lymph nodes [37].

Other European countries have started centralization of gastric cancer surgery as well. In the UK, a National Health plan on many different types of cancer has defined referral regions assigning a certain part of the country to one hospital, thus increasing caseload for these hospitals. Centralization has also been initiated in Finland, Sweden, and the Netherlands. In the Netherlands, gastric surgery is centralized toward hospitals that are already performing esophagectomies in high volumes, thus combining these diseases in specialized upper GI centers.

However, using the hospital volume as the only reason for referral has been criticized as individual low-volume hospitals can have excellent outcomes while high-volume hospitals can have poor outcomes [33]. Therefore, several studies have advocated outcome-based referral, in which patients are referred to hospitals with the best outcomes, rather than hospitals with the highest caseload. In the Western part of the Netherlands, outcome-based referral has been used to improve outcomes for esophagectomy, and has resulted in a decrease in postoperative mortality from 12 to 4 % [49]. Other groups have been searching for processes associated with good outcomes, and the way to initiate these processes in centers with poor outcomes. This, however, is rather difficult as many factors contribute to patient outcomes [50].

One study suggests that combining centralization with auditing brings a stronger improvement in outcomes than centralization without auditing [51]. With auditing, data are collected in a central registry, and health care providers receive feedback on their performance. Several countries have implemented national auditing programs, including the National Oesophagogastric Cancer Audit in the UK, the National Surgical Quality Improvement Program in the USA, as well as several other European countries, which are currently working on a European Upper GI Cancer Audit (EURECCA Upper GI).

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Open Methods of Resection and Reconstruction for Subtotal and Total Gastrectomy

14

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List of Abbreviations

CT	Computed tomography
EUS	Endoscopic ultrasonography
GIA	Gastrointestinal anastomosis
MAGIC	Medical Research Council Adjuvant Gastric Infusional Chemotherapy Trial
NCCN	National Comprehensive Cancer Network
PET	Positron emission tomography
TA	Thoracoabdominal

Overview

The previous chapters of this book have described the epidemiology, pathologic classification, staging, and adjuvant/neoadjuvant treatment of gastric cancer. Accurate preoperative staging of gastric cancer is of paramount importance: staging determines the extent of resection required and helps guide the preoperative consent process. As gastric resection of peptic ulcer disease complications has diminished drastically in the past 20 years, the majority of distal and total gastrectomies are performed for malignancy.

Two prospective randomized clinical trials have demonstrated the equivalence of total versus subtotal gastrectomy for resecting cancer of the distal stomach [1, 2]. The preferred technique for resecting cancer of the proximal stomach, however, remains a controversial topic. Most surgeons favor total gastrectomy to minimize the risk of bile reflux and gastroparesis, but surgeons who favor proximal gastrectomy have reported that this technique has similar complication rates and survival compared with total gastrectomy [3]. A recent systematic review and meta-analysis demonstrated that patients who underwent proximal gastrectomy for gastric cancer had higher rates of tumor recurrence, reflux esophagitis, and anastomotic stenosis than did patients who underwent total gastrectomy [4]. Based on current surgeon preference, concerns over disabling bile reflux with proximal gastrectomy, and the lack of reported benefit in quality of life or oral intake with proximal gastrectomy compared to total gastrectomy, surgeons at our institution do not currently perform proximal gastrectomy. This chapter will focus on the surgical techniques used in subtotal gastrectomy to resect cancers of the distal stomach and in total gastrectomy to resect cancers of the proximal stomach.

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Preoperative Assessment

Assessment begins with a history and physical to include information about presenting symptoms, weight loss, comorbidities, previous surgical history, and physical examination. Although metastasis to distant lymph nodes detected on physical exam are often described in clinical textbooks yet seldom seen in clinical practice, the physical examination should include an assessment of supraclavicular lymph nodes to identify distant lymph node involvement. The baseline laboratory evaluation should include a complete blood count, blood chemistry and renal profile tests, and measurement of nutritional indicators (usually albumin and prealbumin levels). The National Comprehensive Cancer Network (NCCN) Guidelines for Treatment of Gastric Cancer is an extensive 93-page document that can help guide the work-up and treatment of patients with newly diagnosed gastric cancer [5]. All gastric cancer patients likely will have undergone an upper gastrointestinal endoscopy and biopsy for diagnosis. The endoscopy results should be reviewed, and endoscopy may need to be repeated for preoperative planning or at the time of endoscopic ultrasound (EUS).

The modalities available for preoperative staging of gastric cancer include EUS, computed tomography (CT), positron emission tomography (PET)/CT, and diagnostic laparoscopy with peritoneal washings. The NCCN currently recommends chest/abdominal CT with pelvic CT as clinically indicated, PET/CT, and EUS if no metastatic disease is identified on previous imaging studies. The extent of the preoperative workup can be tailored to local expertise and plans for perioperative, adjuvant, or neoadjuvant therapy. Diagnostic laparoscopy should be given strong consideration owing to the high incidence of detectable metastatic disease in gastric cancer and the recent inclusion of positive cytologic results as an indicator of stage IV disease according to The American Joint Committee on Cancer [6]. The NCCN guidelines recommend that patients with T3 tumors or lymph node metastasis be considered for laparoscopic staging with peritoneal washings.

Neoadjuvant, Perioperative, Adjuvant Therapy Considerations

Patients undergoing resection of gastric cancer have three main choices for chemotherapy and radiation; these choices have been described in other chapters in this book but are briefly discussed here because chemotherapy and radiation treatment plans can affect decisions about the timing of diagnostic laparoscopy, need for a feeding tube, and postoperative course.

The first approach is adjuvant chemoradiotherapy. In the SWOG-directed Intergroup Study 0116, a clinical phase III trial in which 559 patients with ≥T3 tumors and/or node-positive gastric cancer were randomized to observation versus adjuvant radiochemotherapy after R0 resection, adjuvant radiochemotherapy provided significant reduction in overall relapse and locoregional failure [7, 8]. Adjuvant chemoradiotherapy demonstrated an improvement in survival and it is notable that only 65 % of patients assigned to the chemoradiotherapy group completed all protocol treatment. This surgery-first approach is a good choice for patients with bleeding or obstruction and for patients who decline perioperative or neoadjuvant therapy.

The second approach is perioperative chemotherapy. This approach is based on the results of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial [9]. In this approach, patients receive three cycles of epirubicin, cisplatin, and fluorouracil preoperatively and then again postoperatively. In the MAGIC trial, patients who received chemotherapy had higher overall survival rates than did the control group, although only 42 % of patients assigned to the chemotherapy group completed all protocol treatment. The MAGIC approach has several advantages. A high percentage of patients should receive at least the preoperative cycles of chemotherapy, even if these patients are unable to complete all protocol treatment. Radiation may be less effective and not necessary for patients that undergo a more extensive (D2) lymph node dissection. Furthermore, the MAGIC approach allows physicians not only to evaluate patients' response to therapy but also to select patients

with borderline performance status for surgery on the basis of response to chemotherapy.

The third approach, neoadjuvant therapy, delivers induction chemotherapy and chemoradiotherapy before resection. This approach is based on the results of phase II trials from The University of Texas MD Anderson Cancer Center [10–12]. The benefit of this approach is it has a high frequency of patients completing all protocol therapy as the chemotherapy and radiation therapy are given prior to surgery. However, no studies have directly compared the neoadjuvant approach with the other two approaches.

The timing of diagnostic laparoscopy is also important in the context of adjuvant, perioperative, or neoadjuvant therapy. If indicated, laparoscopy can be performed just prior to full exploration in patients undergoing a surgery-first (Intergroup 116) approach, but the perioperative and neoadjuvant therapy approaches require a separate general anesthesia induction for diagnostic laparoscopy. Patients who choose a neoadjuvant therapy approach of induction chemotherapy and chemoradiotherapy should also be considered for feeding tube placement during diagnostic laparoscopy, as feeding tubes are helpful in preventing delays in chemoradiotherapy.

Operative Technique

Diagnostic Laparoscopy Prior to Exploratory Laparotomy

The decision whether to perform a diagnostic laparoscopy immediately prior to full exploration and attempted resection requires a tailored approach. If the patient has already undergone a diagnostic laparoscopy prior to preoperative chemotherapy or chemoradiotherapy, it is our practice only to perform a repeat laparoscopy immediately prior to exploration for patients with suspicious lesions or tumors at high-risk for peritoneal spread.

Enter the abdomen above or below the umbilicus using a sharp open technique for cannula placement and insufflate the abdomen with CO_2.

In most cases, a 5-mm left-sided port is required. This port may be used later to place a feeding tube, if required.

Inspect all peritoneal surfaces. Any ascites should be aspirated and sent for immediate cytologic analysis. Peritoneal washings, if not performed previously, can be collected and analyzed at this time.

Biopsy any abnormal peritoneal lesions. Frozen-section analysis of biopsy specimens typically takes 30 min, and cytologic analysis of ascites or washings typically takes 45 min.

Exploratory Laparotomy

Exploration of the abdomen prior to resection is indicated in patients undergoing potentially curative resection.

Enter the abdomen through a midline incision.

If desired, preserve the length of the falciform ligament for subsequent flap placement over the duodenal stump.

Expose the appropriate area of the abdomen, typically using a Thompson retractor.

Fully explore the abdomen to evaluate areas not visualized during the laparoscopy.

Consider preserving the greater omentum to create an omental pedicle flap based on the right or left gastroepiploic artery to reinforce the gastrojejunostomy or the esophagojejunostomy.

Subtotal Gastrectomy

Subtotal gastrectomy may be considered for patients who have tumors of the distal body and antrum and who have a preoperative assessment suggesting an adequate tumor-free margin can be achieved proximally and an adequate amount of stomach will remain for reconstruction.

Separate the greater omentum from the transverse mesocolon; if desired, preserve the blood supply for an omental pedicle flap based on the splenic vessels. Dissect the avascular plane between the greater omentum and the transverse mesocolon to the level of the pancreas (Fig. 14.1).

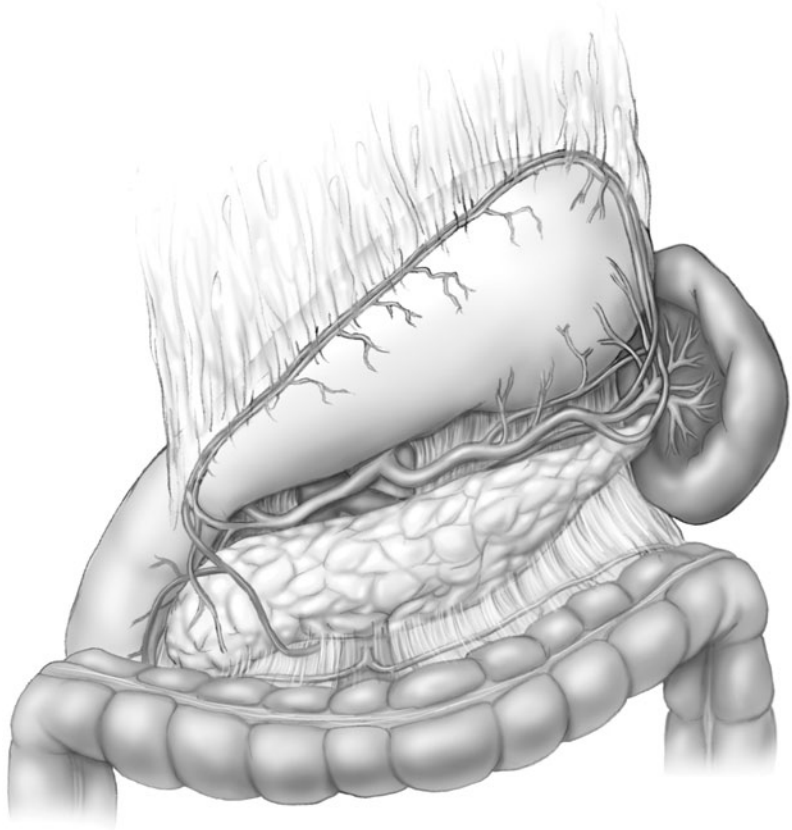

Fig. 14.1 Dissection of the avascular plane between the greater omentum and the transverse mesocolon during gastrectomy. (Image courtesy of Paul F. Mansfield, MD)

Mobilize the greater curve by dividing the gastrocolic omental tissue outside of the gastroepiploic vessels to the planned point of transection of the proximal stomach. Extending the area of dissection to the left will help facilitate the exposure and dissection of the gastroepiploic vessels.

Trace the middle colic vessels down to the gastrocolic trunk to identify the right gastroepiploic vessels. Lymphatic tissue and identifiable lymph nodes often must be removed to identify the gastroepiploic vessels and can be swept toward the pylorus with the specimen or can be removed and labeled separately.

Ligate the gastroepiploic vein and artery with 2–0 or 3–0 silk, and place an additional 4–0 polyprolene suture on the proximal aspect of the artery to provide hemostatic security. Divide the right gastroepiploic vessels.

Isolate, ligate, and divide the right gastric vessels close to the proper hepatic artery.

Isolate the duodenum. Often a few additional small feeding vessels must be ligated and divided. Ligate the duodenum with a 3.5-mm thoracoabdominal (TA) stapler, and transect the duodenum with a knife. Alternatively, use a gastrointestinal anastomosis (GIA) stapler or sharp transection with handsewn closure to transect the duodenum (Fig. 14.2).

Obtain a specimen from the duodenal margin, and send for immediate frozen-section analysis to document a negative surgical margin.

Transect the thin avascular portion of the lesser omentum (Fig. 14.3). Guided by preoperative

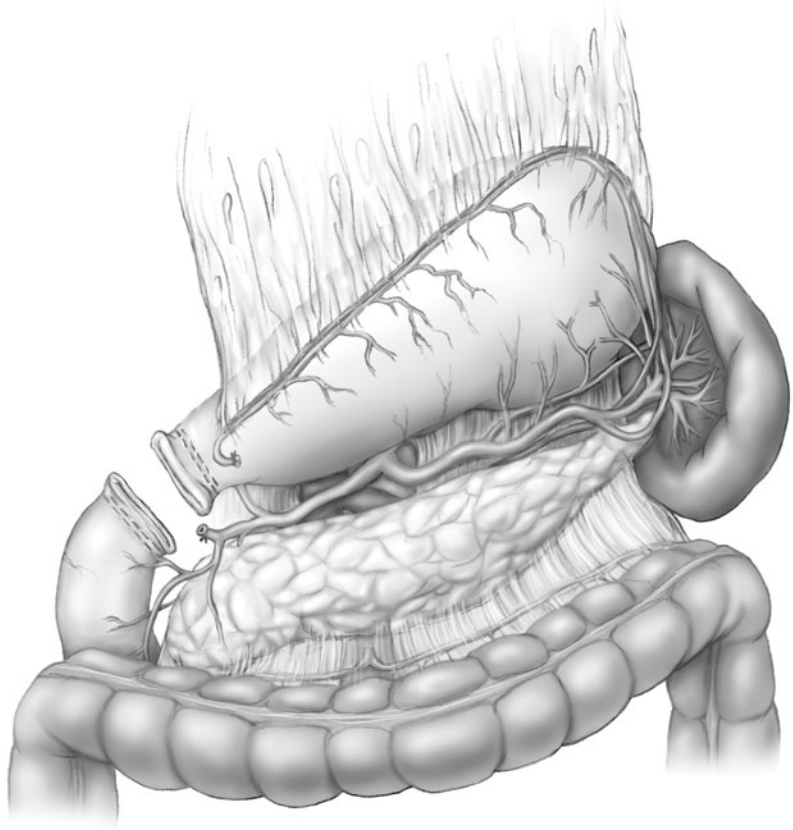

Fig. 14.2 Isolation, ligation, and transection of the duodenum during a subtotal gastrectomy. (Image courtesy of Paul F. Mansfield, MD)

imaging, take care to identify a potential accessory or replaced left hepatic artery.

Isolate, ligate, and transect the left gastric vessels. The left gastric vessel dissection can be initiated with anterior and cephalad retraction of the stomach. The left gastric vein (the coronary vein of the stomach) often is encountered surgically after the point at which it receives branches from the anterior and posterior lesser curvature but before the vein terminates in the portal vein. Ligate the left gastric vein with 3–0 silk. Variable amounts of celiac nodal tissue will be encountered prior to identification of the left gastric artery. The left gastric artery is identified most often in the middle of the celiac trunk. Ligate the left gastric artery with 2–0 or 3–0 silk, and place an additional 4–0 polypropylene suture on the proximal aspect of the left gastric artery to provide hemostatic security.

Identify a suitable area for transection of the proximal stomach. To help obtain a negative surgical margin, thoroughly review preoperative and pretreatment imaging and endoscopy results, use intraoperative palpation, and perform intraoperative endoscopy.

Transect the proximal stomach with a 4.8-mm GIA stapler. Alternatively, divide the stomach between bowel clamps, or ligate the stomach with a TA stapler and transect the specimen with a knife (Fig. 14.4).

Remove the specimen staple line, deliver to pathology, and orient the specimen for the pathologist. Consider the gastric cancer histologic type (intestinal versus diffuse) when deciding

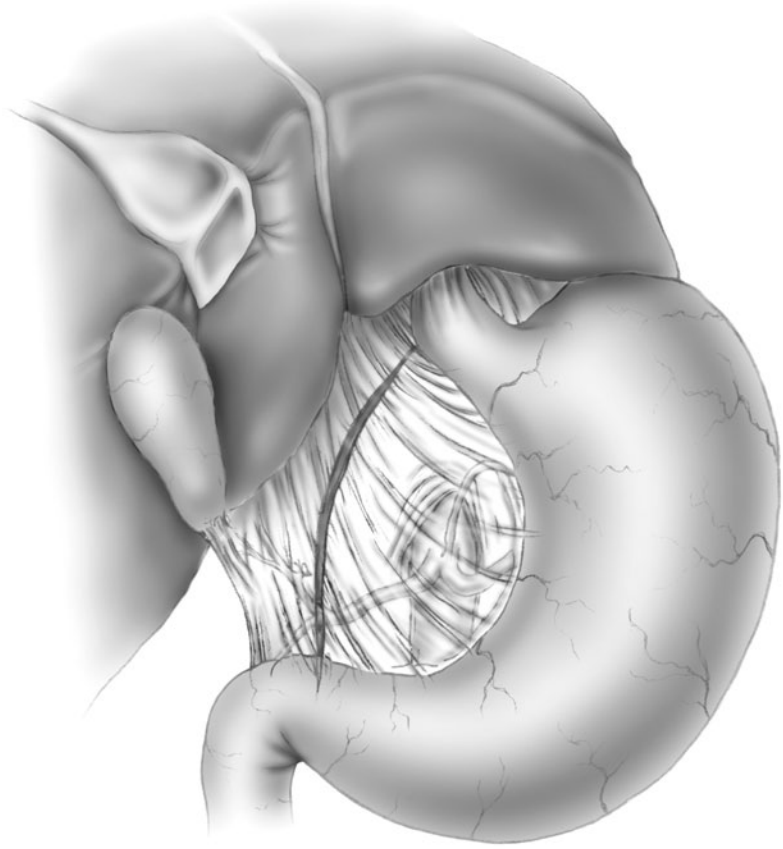

Fig. 14.3 Transection of the avascular portion of the lesser omentum during a subtotal gastrectomy. (Image courtesy of Paul F. Mansfield, MD)

whether to obtain circumferential or focused gastric margin specimens for intraoperative analysis.

While waiting for histologic confirmation of negative surgical margins along the proximal gastric staple line, which can be time-consuming if the entire gastric margin is examined, dissect the D2 lymph nodes (Fig. 14.5).

Irrigate the abdomen, and confirm hemostasis.

Perform reconstruction with a Billroth II loop gastrojejunostomy or a Roux-en-Y gastrojejunostomy (both described below).

Billroth II Loop Gastrojejunostomy

In general, oversew a portion of the lesser curvature staple line with 3–0 silk Lembert sutures not only to reinforce an area that could be at high risk for leakage but also to limit the size of the upcoming anastomosis, as a full-length gastrojejunostomy is unnecessary.

Create a defect in the transverse mesocolon, and perform the anastomosis in a retrocolic fashion.

For a handsewn anastomosis, approximate the afferent limb of the small bowel to the greater curvature of the stomach and the efferent limb to the lesser curvature.

Alternatively, create a stapled anastomosis to the posterior stomach. Approximate the small bowel to the posterior stomach with 3–0 silk sutures at the corners of the anastomosis. Create a defect in the stomach and small bowel, perform a stapled side-to-side anastomosis with a GIA blue

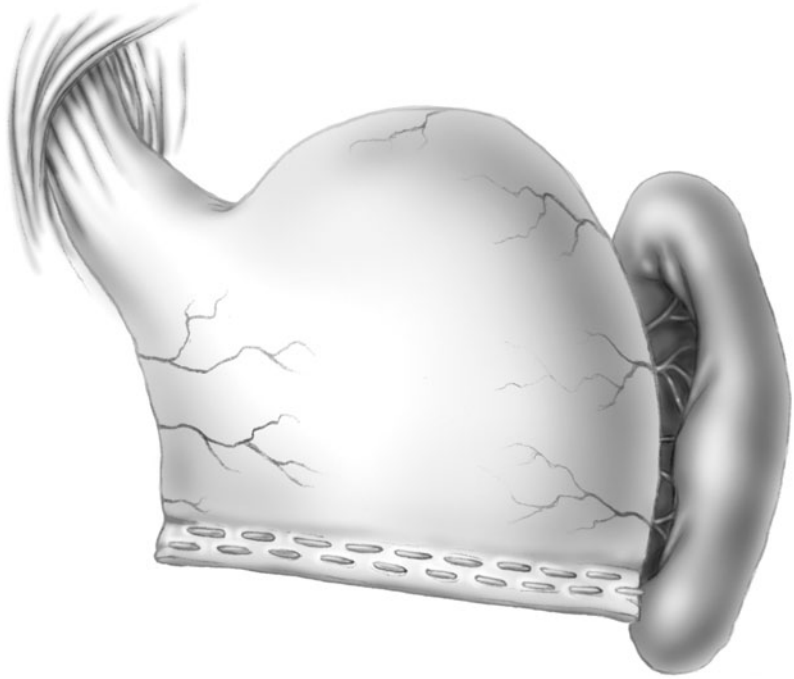

Fig. 14.4 Transection of the proximal stomach during a subtotal gastrectomy. (Image courtesy of Paul F. Mansfield, MD)

or green stapler, and close the gastroenterotomy defect.

Roux-en-Y Gastrojejunostomy

Use a blue GIA stapler to transect the first redundant limb that is suitable for limb creation distal (often approximately 20 cm) to the ligament of Treitz.

Using transillumination, take down the mesentery to identify feeding vessels and to determine the length necessary to prevent anastomotic tension.

Create a defect in the transverse mesocolon to the left of the middle colic vessels, and place the roux limb into position. Confirm that the roux limb is tension-free.

Create a 60-cm limb by performing either a handsewn or stapled jejunojejunostomy.

Oversew a portion of the lesser curvature staple line with 3–0 silk lembert sutures.

After confirming roux limb viability, perform either a handsewn or stapled gastrojejunostomy (Fig. 14.6).

Total Gastrectomy

When it is not clear preoperatively whether a total gastrectomy or an Ivor Lewis esophagectomy is required for tumors of the gastroesophageal junction, maintain the blood supply from the right gastroepiploic and right gastric vessels until the esophageal margin is cleared for a total gastrectomy.

Separate the greater omentum from the transverse mesocolon; if an omental pedicle flap is desired, maintain the blood supply from the right gastroepiploic or splenic vessels.

Mobilize the greater curvature by ligating the short gastric vessels.

Transect the left triangular ligament, and retract the liver laterally.

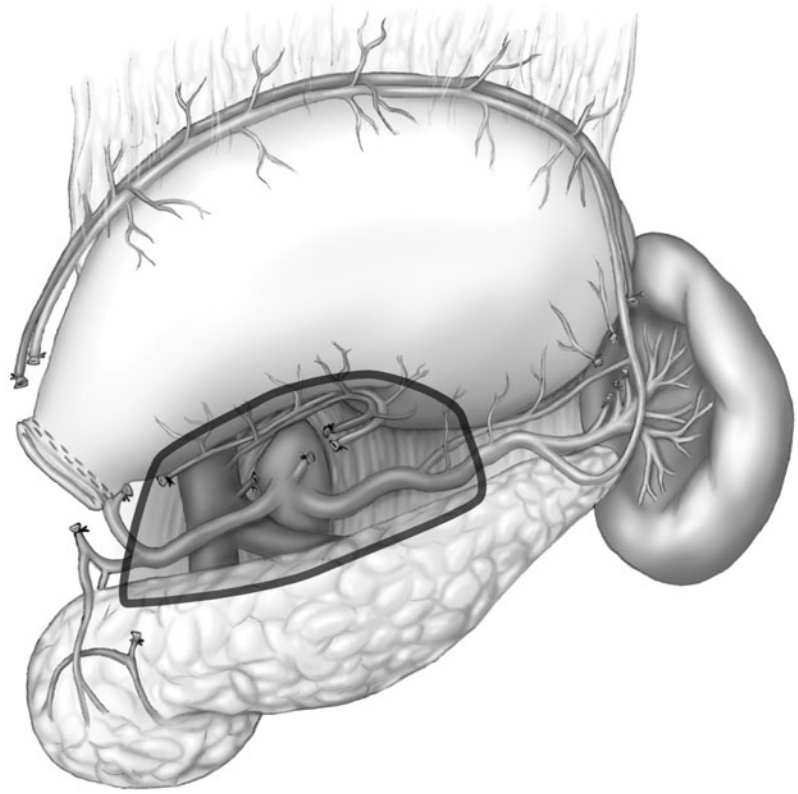

Fig. 14.5 D2 lymph node dissection during a subtotal gastrectomy. (Image courtesy of Paul F. Mansfield, MD)

Lyse the attachments between the esophagus and right and left crus.

Transect the lesser omentum.

After using a sharp technique for circumferential dissection of the esophagus, encircle the esophagus with a Penrose drain.

Mobilize the esophagus to obtain the desired length.

To gain additional esophageal length and visualization, transect the crus, transect the anterior diaphragm, or use hand-held retractors.

Place a Satinsky clamp high in the esophageal hiatus to prevent esophageal retraction.

Transect the esophagus.

Obtain a specimen from the esophageal margin, and perform frozen-section analysis immediately.

Place stay sutures to prevent separation of the layers of the esophageal wall and to prevent retraction before the removal of the Satinsky clamp.

Isolate, ligate, and transect the left gastric vein and artery.

Once the frozen-section analysis results for the esophageal margin indicate that an esophagectomy will not be necessary, isolate, ligate, and divide the right gastroepiploic vessels.

Transect the right gastric vessels.

Staple the duodenum with a blue TA stapler, and transect the duodenum with a knife; alternatively, ligate and transect the duodenum with a GIA stapler.

Obtain a duodenal margin specimen, and send it for immediate frozen section analysis.

While waiting for histologic confirmation of negative surgical margins, dissect the D2 lymph nodes, if necessary.

Irrigate the abdomen and confirm hemostasis.

Perform reconstruction with a 60-cm Roux-en-Y anastomosis.

Use a blue GIA stapler to transect the jejunum approximately 20 cm distal to the ligament of

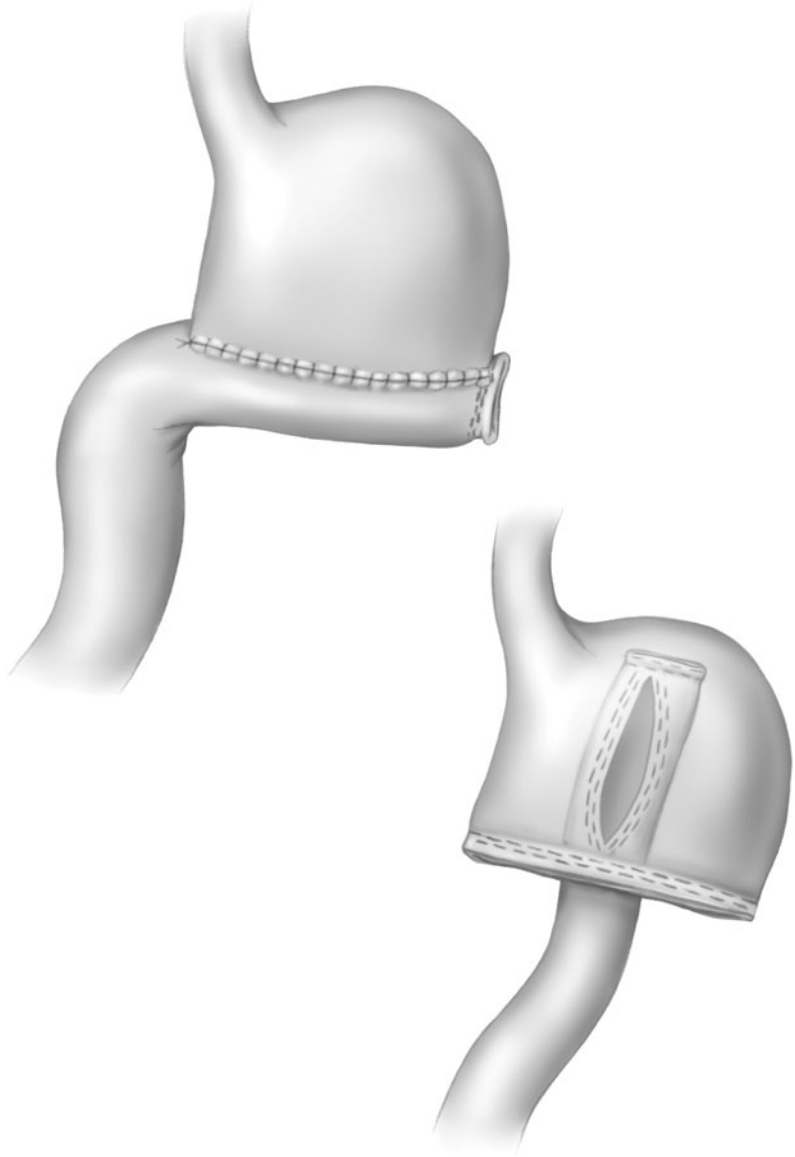

Fig. 14.6 Roux-en-Y gastrojejunostomy as part of a subtotal gastrectomy. (Image courtesy of Paul F. Mansfield, MD)

Treitz. Pay careful attention to the length of the jejunal mesentery; select an appropriate site that has enough length to prevent tension in reaching the esophagus.

Create a defect in the mesocolon to the left of the middle colic vessels.

Transect the mesentery of the roux limb to allow for tension-free placement into the upper abdomen.

Perform either a handsewn or stapled jejunojenjunostomy to create a 60-cm roux limb.

Inspect the roux limb, and confirm good viability and blood supply.

Perform an esophagojejunostomy using either a handsewn method or a stapled end-to-side technique (Fig. 14.7).

Place a nasogastric tube approximately 10–15 cm distal to the anastomosis.

Perform an air leak test after completing the anastomosis.

Irrigate the abdomen again, and confirm hemostasis.

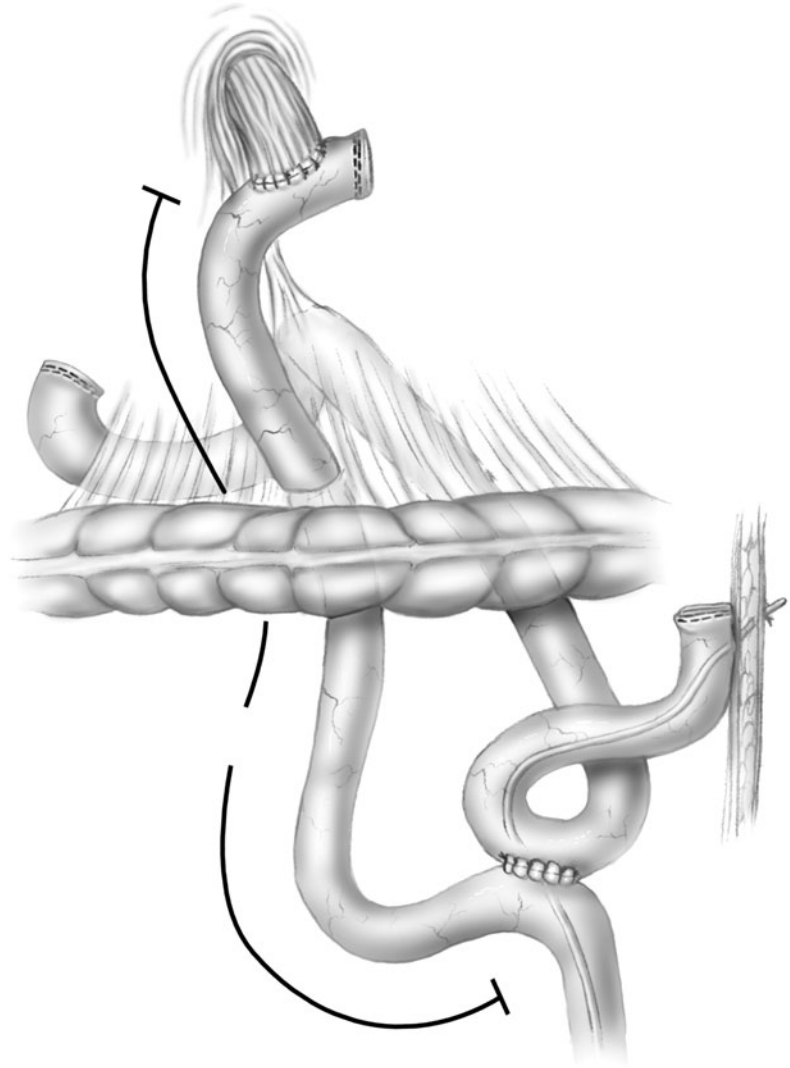

Fig. 14.7 Esophagojejunostomy during a total gastrectomy. (Image courtesy of Paul F. Mansfield, MD)

Place the omental pedicle flap around the esophagojejunostomy, and secure the falciform ligament flap over the duodenal stump.

Consider placing a drain not only to diagnose and treat esophagojejunal leakage but also to treat pancreatic fluid leakage after the D2 lymph node dissection.

Place a feeding tube 15 cm distal to the jejunojejunostomy. Form a small Witzel tunnel, taking care not to compromise the bowel lumen, as an obstruction at this level can compromise the integrity of the jejunojejunostomy and the duodenal stump staple line. An alternate method to place the feeding tube without narrowing the small bowel is demonstrated in Fig. 14.7.

Postoperative Management

After undergoing subtotal gastrectomy, patients often require a nasogastric tube for 2–3 days. Once the nasogastric tube has been removed, patients can begin a liquid diet and slowly advance to a regular diet.

After undergoing total gastrectomy, patients require a nasogastric tube for 3 days; the tube is then removed if patients are doing well.

An upper gastrointestinal contrast study is not performed unless there is clinical suspicion of a leak.

Tube feeding, if necessary, is started on postoperative day 2; patients are slowly advanced according to their clinical status. Patients are monitored closely for distention or inability to tolerate tube feeding.

Patients are maintained on deep vein thrombosis prophylaxis for 4 weeks, in accordance with the American College of Chest Physicians guidelines for preventing venous thromboembolism in nonorthopedic surgical patients [13].

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15 Laparoscopic Methods of Resection and Reconstruction for Subtotal and Total Gastrectomy with D2 Lymphadenectomy

Han-Kwang Yang and Do Joong Park

Introduction

Since Kitano performed the first laparoscopy-assisted distal gastrectomy for early gastric cancer in 1991 [1], laparoscopic gastrectomy has become an alternative option for the treatment of gastric cancer. With advances in instrumentation and accumulation of laparoscopic experience, a variety of different laparoscopic techniques have been introduced and laparoscopic gastrectomy is now used for less invasive but highly technically demanding procedures, such as para-aortic lymphadenectomy and remnant gastric cancer [2–5].

Currently, there is a trend for resection and reconstruction after laparoscopic distal or total gastrectomy to be performed using totally laparoscopic procedures rather than laparoscopy-assisted procedures. Various intracorporeal anastomoses have been introduced, such as delta-shaped anastomosis, the beta-shaped anastomosis, and the overlap method using a linear stapler.

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Safety of Radical Laparoscopic Gastrectomy

Laparoscopic Gastrectomy for Early Gastric Cancer

Laparoscopic surgery for early gastric cancer has gained popularity in recent years due to evidence from six prospective randomized controlled trials [6–11]. However, the majority of these trials were limited by a small sample size, the use of patients from a single center, and a short-term follow-up period.

Currently, two large-scale multicenter randomized controlled trials are underway to elucidate the long-term oncological results of laparoscopic gastrectomy: The Korean Laparoscopic Gastrointestinal Surgery Study (KLASS)-01 trial and the Japanese Clinical Oncology Group (JCOG) 0912 trial. The KLASS-01 trial is the first multicenter randomized controlled trial to compare open and laparoscopic gastrectomy in patients with clinical stage T1-T2N0 gastric cancer from 15 institutions. From 2006 to 2010, 1416 patients were enrolled, and the final results are expected in 2015 [12]. In 2010, the JCOG also started a multicenter randomized controlled trial (JCOG 0912) to compare open distal gastrectomy and laparoscopy-assisted distal gastrectomy in 920 patients with stage I gastric cancer recruited from 33 institutions [13].

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Laparoscopic Gastrectomy for Advanced Gastric Cancer

There is considerable interest in the use of laparoscopic gastrectomy to treat advanced gastric cancer. As surgeons accumulate experience with laparoscopic gastrectomy, some are extending the indication of laparoscopic gastrectomy to locally advanced gastric cancer. Laparoscopic gastrectomy may also be feasible for advanced gastric cancer. Choi et al. conducted a meta-analysis of one randomized controlled trial and nine nonrandomized controlled trials with 1819 patients with advanced gastric cancer (960 patients in the open group and 859 patients in the laparoscopy group), and reported that there was no statistical difference in overall survival and disease-free survival between the two groups [14]. Shinohara et al. performed a retrospective cohort study of 336 patients who underwent gastrectomy with D2 lymph node dissection for cT2-T4 cancer. Of the 336 patients, 150 underwent open gastrectomy and 186 underwent laparoscopic gastrectomy. The laparoscopic D2 procedure was associated with significantly less operative blood loss and shorter hospital stay than the open procedure, but there was no difference in morbidity and mortality between the two procedures. The 5-year disease-free and overall survival rates were 65.8 and 68.1% in the laparoscopic group, respectively, and 62.0 and 63.7% in the open group, respectively ($p=0.737$ and $p=0.968$, respectively, for comparison across group). Moreover, there was no difference in the pattern of recurrence between the two groups. In the laparoscopic group, 53 patients (28.5%) developed tumor recurrence: of which 29 (54.7%) were peritoneal recurrences, 23 (43.4%) were distant or hematogenous recurrences, and 15 (28.3%) were locoregional or lymphatic recurrences. In the open group, 34 patients (22.7%) developed tumor recurrence, of which 17 (50.0%) were peritoneal recurrences, 15 (44.1%) were distant or hematogenous recurrences, and 11 (32.6%) were locoregional or lymphatic recurrences [15]. Park et al. reported the long-term outcomes of 239 patients who underwent laparoscopic gastrectomy for advanced gastric cancer [16]. These patients were part of a multicenter retrospective study and were preoperatively diagnosed with early gastric cancer but diagnosed with advanced gastric cancer on final pathological examination. The overall 5-year survival rates were 90.5% for patients with stage IB cancer, 86.4% for stage IIA, 52.8% for stage IIIA, 52.9% for stage IIIB, and 37.5% for stage IIIC, and these survival rates are comparable to the 5-year survival rate reported for open gastrectomy. Lee et al. reported the short-term outcomes of a prospective phase II trial of 157 patients with cT2N0-T4aN2 gastric cancer. The mean number of retrieved lymph nodes was 52.7 for laparoscopy-assisted distal gastrectomy and 63.8 for laparoscopy-assisted total gastrectomy. The complication rate was 25.5% and local and systemic complication rates (more than grade II on the Clavien-Dindo classification) were 8.3 and 3.2%, respectively. Lee et al. concluded that laparoscopic gastrectomy with D2 lymph node dissection was safe and technically feasible for the treatment of advanced gastric cancer, with an acceptable rate of morbidity and mortality [17].

At present, there are three large-scale multicenter trials underway on the use of laparoscopic gastrectomy to treat advanced gastric cancer, in Korea, Japan, and China. In Korea, the KLASS-02 trial is a phase III study to evaluate the efficacy of laparoscopy-assisted distal gastrectomy with D2 lymph node dissection for the treatment of advanced gastric cancer. The estimated sample size is 1050 and the primary endpoint is 3-year disease-free survival. For quality control, all surgeons are standardized and qualified through a review of six unedited videos of their procedures (three laparoscopic and three open procedures) by independent reviewers. The Japanese Laparoscopic Surgery Study Group (JLSSG) launched a multicenter phase II/III study, entitled JLSSG 0901, to compare laparoscopy-assisted distal gastrectomy and open distal gastrectomy in patients with cT2-T4aM0 gastric cancer. The incidence of major complications will be assessed after the recruitment of 180 patients. If an early-stopping rule related a high complication rate is not invoked, the trial will continue until 500 patients

are enrolled [18]. Recently, the Chinese Laparoscopic Gastrointestinal Surgical Study (CLASS) group started a phase III study, entitled CLASS-01 and the study design is similar to that of the KLASS-02 trial.

Current Status of Oncologic Safety

A large-scale multicenter retrospective study of 1477 patients' laparoscopic procedures and 1499 open procedures was conducted between April 1998 and December 2005 by Kim and nine of the surgeons who are participating in the KLASS-01 clinical trial. Recently, they reported the long-term results obtained after a follow-up period of more than 70 months, and they showed that overall survival, disease-specific survival, and recurrence free survival were not statistically different between open and laparoscopy groups at any cancer stage. In matched analysis, the morbidity was 15.1 % in the open group and 12.5 % in the laparoscopic group ($p = 0.184$) and the mortality rate was 0.3 % in the open group and 0.5 % in the laparoscopic group ($p = 1.000$) [19].

The D2 Lymphadenectomy Technique for Laparoscopic Distal Gastrectomy

Dissection of the Greater Curvature and Left Gastroepiploic Vessels (Stations 4sb and 4d)

Pneumoperitoneum and port placements are established (Fig. 15.1a, b), and surgery starts with division of the greater omentum, beginning from the center and moving to the left. The division of the greater omentum starts 3–4 cm from the gastroepiploic arcade for early gastric cancer (total omentectomy for advanced gastric cancer) continued toward the lower pole of the spleen and the tail of the pancreas to the origin of left gastroepiploic vessels. The left gastroepiploic vessels are carefully dissected and ligated using clips near their origin just anterior to the pancreas (Fig. 15.2a). The end of the left gastroepiploic arcade is identified and the omentum is divided from the gastric wall from proximal to distal.

Dissection of the Infrapyloric Lymph Nodes (Station 6)

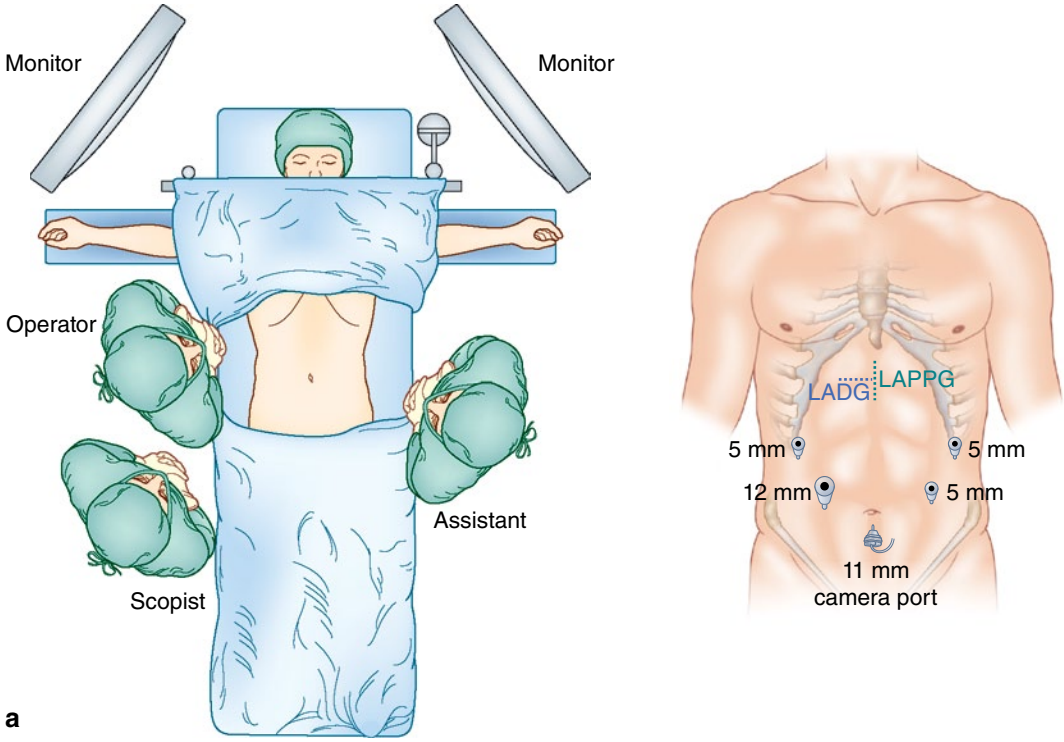
The division of the greater omentum is continued toward the hepatic flexure. The assistant retracts the stomach antrum with right hand instrument and counter traction of mesocolon with left hand instrument (Fig. 15.2b). This maneuver improves the operation field so that the operator can identify the infrapyloric anatomy. The infrapyloric dissection is performed using ultrasonic coagulating shears and should be performed carefully to avoid the tearing of small vessels that leads to troublesome bleeding. The right gastroepiploic vein is identified, ligated, and divided at its origin from the gastrocolic trunk (Fig. 15.2c–e). The right gastroepiploic artery is also divided at its origin from the gastroduodenal artery (GDA) and the infrapyloric branches are then divided to expose the bulb of the duodenum. After then, dissection continues along the GDA until GDA meet common hepatic artery (Fig. 15.2f, g).

After dissection of the posterior side of first portion of duodenum, gauze is inserted in the posterior surface of duodenum (Fig. 15.2h). This maneuver protects underlying vessels during supraduodenal dissection.

During this dissection, hanging method of the stomach using monofilament suture through the abdominal wall can facilitate visualization and dissection of the suprapancreatic area if BI reconstruction or pylorus preserving gastrectomy is planned (Fig. 15.2i, j) [20].

Dissection of the Suprapyloric Lymph Nodes and the Hepatoduodenal Ligament Along the Proper Hepatic Artery (Stations 5 and 12a)

For the suprapyloric dissection, the assistant's right hand is grasping right gastric artery pedicle and left hand presses downward on the pylo-



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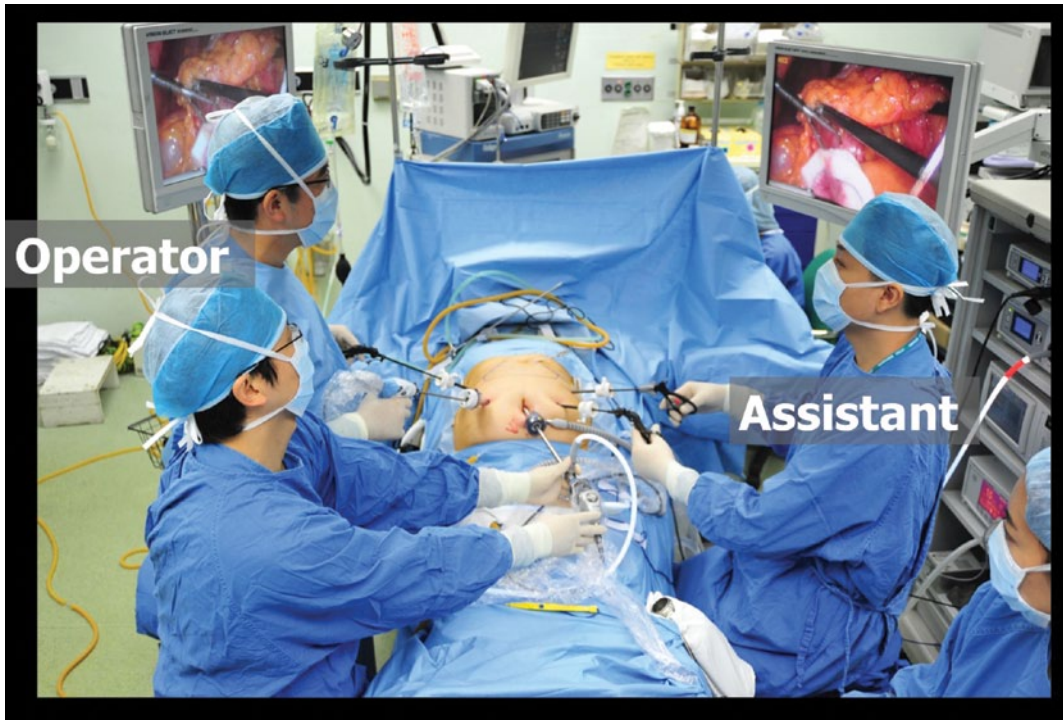

b

Fig. 15.1 **a** Operation setup and port placement for laparoscopic distal gastrectomy. **b** Actual operation setup

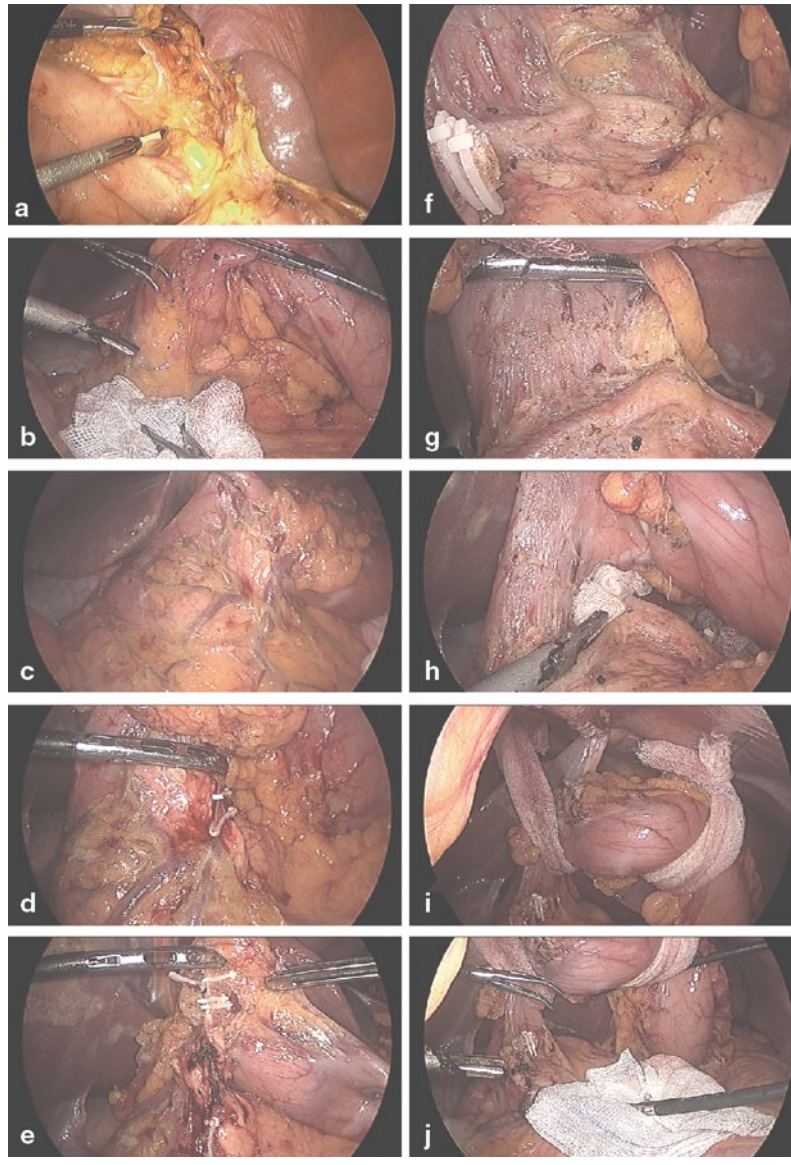

Fig. 15.2 Dissection of greater curvature side of the stomach. Dissection of *left* gastroepiploic vessels at their origin. Setup for dissection of infrapyloric area; notice the assistant's *right* hand **a** is lifting antrum and the *left* hand **b** is push down mesocolon with a gauze, which facilitate separation of omentum from fused mesocolon. **c** Anterior surface of pancreas head and 2nd portion of duodenum are exposed. **d** Dissection of *right* gastroepiploic vein. **e** Dissection of *right* gastroepiploic artery. **f** and **g** Dissection of duodenum along the gastroduodenal artery. **h** Put gauze behind *right* gastric artery pedicle. **i** and **j** Hanging stomach using gauze strips around antrum and lower body to facilitate exposure of supra-pancreatic node dissection

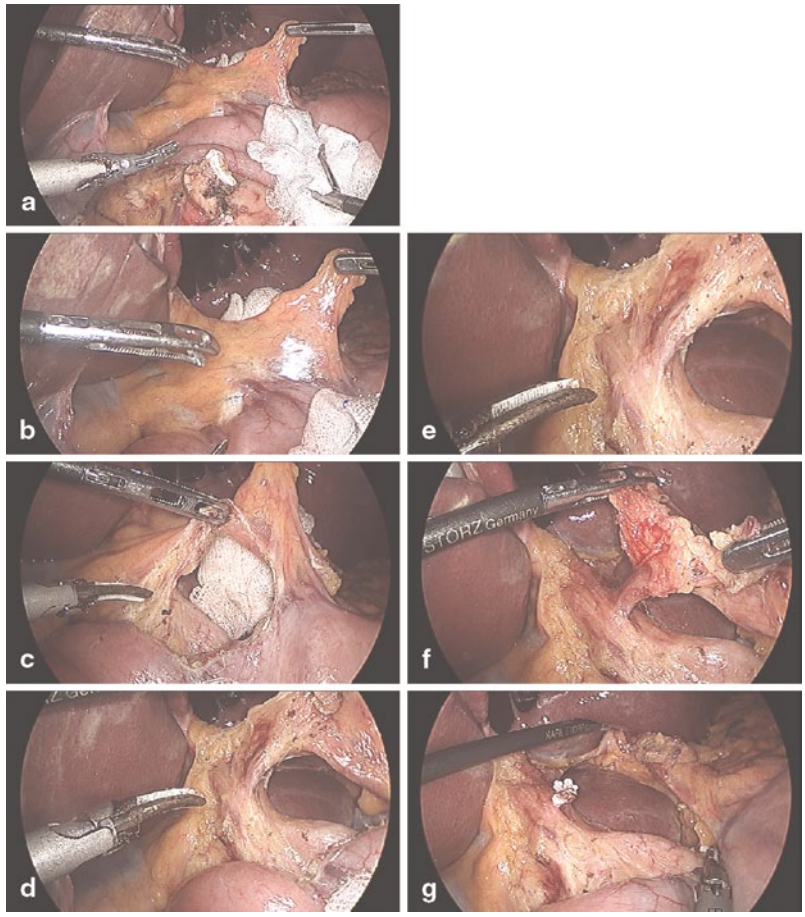

Fig. 15.3 Supra-pyloric dissection **a**–**c** the gauze put behind *right* gastric artery (see Fig. 15.2h) is visible and serves as a safe guard to guide dissection along the 1st portion of duodenum also protect underlying arteries such as gastroduodenal artery. **d**–**f** Dissection continues the *right* side of hepatic artery proper (#12a LN) and along the *right* gastric artery (#5 LN). **g** *Right* gastric artery is ligated and transected

rus with a grasper over a gauze (Fig. 15.3a, b). The space between right gastric artery and first part of duodenum is divided carefully over the gauze which was put under the duodenum (see Fig. 15.2h). Once this space is opened, the GDA is exposed. Continue dissection along the right side of the hepatic artery and lymph node tissue are pulled off along the vessel to the left side of the patient to enable complete dissection of the station 12a lymph nodes (Fig. 15.3c, d, e, f, g). After ligation and division of the right gastric artery, the duodenal bulb is mobilized and transected distal to the pylorus for Billroth II.

Dissection of the Common Hepatic Artery and Celiac Axis (Stations 7, 8a, and 9)

The pedicle of the left gastric vessels is carefully lifted by the assistant's right hand and the pancreas is carefully pressed downward by the assistant's left hand (Fig. 15.4a, b). The dissection of common hepatic artery begins by opening up the peritoneum that overlies the superior border of the pancreas and proceeds from the common hepatic artery to the root of the posterior gastric artery using ultrasonic coagulating shears. After

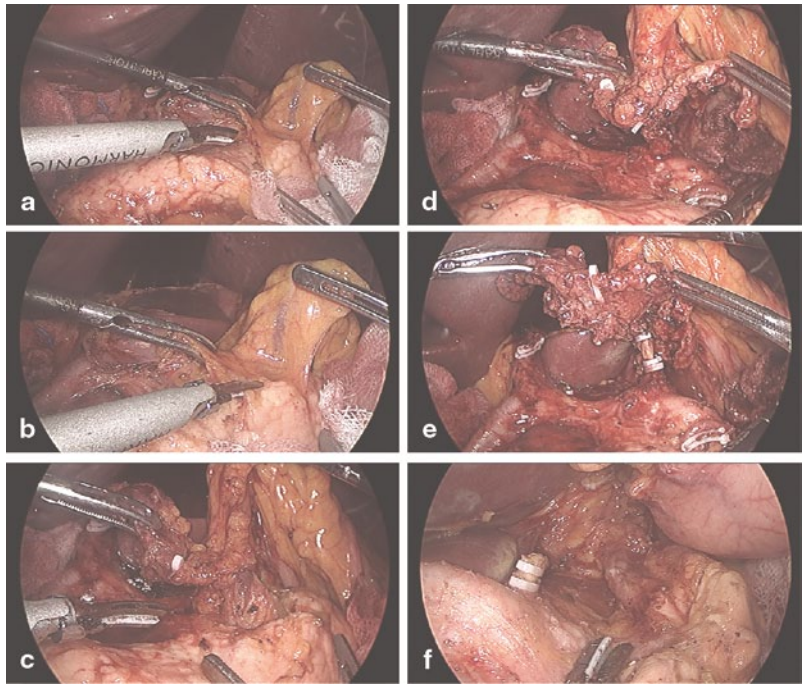

Fig. 15.4 Supra-pancreatic area dissection. **a**–**e** Setup for the supra-pancreatic node dissection; (**a**) the assistant's *right* hand (*R*) is lifting left gastric vessels pedicle and the *left* hand (*L*) is push down pancreas with a gauze, (**f**) #11p LN dissected along the splenic artery and vein

dissection and division of the left gastric artery and vein, all the nodal tissue around the celiac axis should be swept off the retroperitoneum (Figs. 15.4c, d, f).

Dissection of the Splenic Artery (Station 11p)

After division of the left gastric artery, the soft tissue around the proximal portion of the splenic artery and vein is dissected and removed en bloc until the proximal half of the splenic artery (Fig. 15.4f). During this procedure, the assistant provides downward counter retraction of the pancreas (to evert the upper border of pancreas). Dissection is performed using ultrasonic coagulating shears and should be performed carefully to avoid bleedings from rich small vessels around the splenic vessels that frequently lead to minor bleeding.

Dissection of the Right Paracardial Nodes and Lesser Curvature (Stations 1 and 3)

The upper border of the right paracardia is the junction of the cutting line of the lesser omentum and the right crus of the diaphragm. All the soft tissue around this region should be taken off, and removal of the soft tissue proceeds from the oral side to the anal side along the lesser curvature. It is helpful if the assistant lifts and retracts the soft tissues against the gastric wall during this procedure (Fig. 15.5a, b, c).

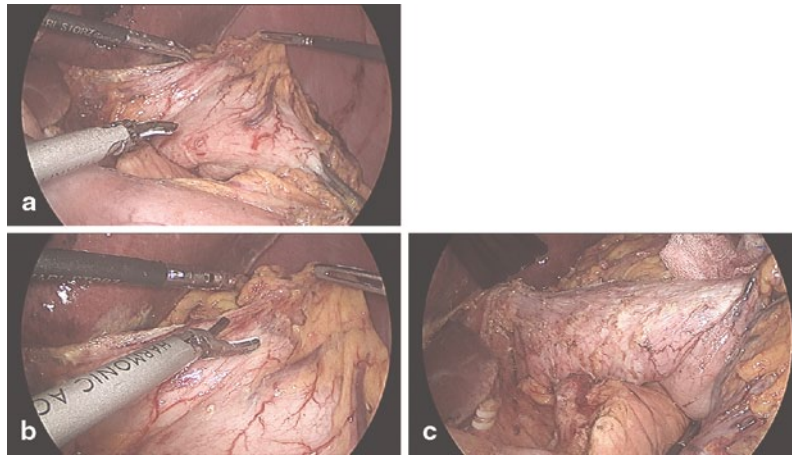

Fig. 15.5 LN dissection along the lesser curvature of cardia and upper stomach. **a**–**c** dissection from posterior side of lesser curvature to anterior side

D2 Lymphadenectomy Technique for Laparoscopic Total Gastrectomy

Dissection of the Left Paracardial Area and Short Gastric Artery (Stations 2 and 4sa)

The esophagus is adequately mobilized and transected for laparoscopic total gastrectomy. After transection of the esophagus, the assistant rolls the distal esophageal stump and upper stomach caudally toward the dorsal side of the upper stomach. The esophagocardiac branch of the left inferior phrenic artery is divided at its origin to enable complete dissection of the station 2 lymph nodes. Dissection continues toward the phrenoesophageal membrane and the splenophrenic ligament and finally the posterior surface of the upper stomach is separated from the retroperitoneum.

Dissection of the Splenic Hilum and the Distal Splenic Artery (Stations 10 and 11d)

Dissection of the distal splenic artery continues from the proximal splenic artery to the splenic hilum (Fig. 15.6a). The splenic artery and vein should be exposed and the soft tissue around the vessels and splenic hilum is carefully dissected with ultrasonic coagulating shears to avoid thermal injury that leads to troublesome postoperative pseudoaneurysm (Fig. 15.6b).

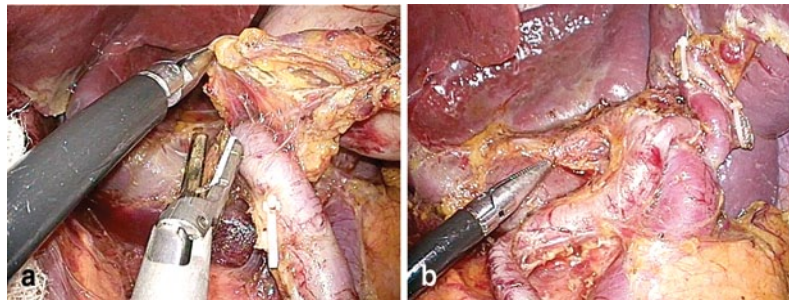

Fig. 15.6 Laparoscopic total gastrectomy with D2 lymphadenectomy. **a** Dissection around distal splenic artery. **b** Dissection of splenic hilum

Reconstruction by Billroth I Method after Laparoscopic Distal Gastrectomy

Gastroduodenostomy performed using a Billroth I method is one of the most common types of reconstruction after laparoscopic distal gastrectomy. Billroth I anastomosis preseves the physiologic duodenal passage of food and avoids gastrojejunostomy-related complications such as afferent loop syndrome or Petersen's hernia. Gastroduodenostomy performed using a Billroth I method is relatively simple and faster than reconstruction performed using Billroth II or Roux-en-Y methods.

Extracorporeal End-to-End Modified Double Stapling Method

For extracorporeal end-to-end modified double stapling, a 4–5 cm length of transverse mini-laparotomy is made on the right upper epigastrium of the abdomen. The duodenum is retrieved and clamped using a purse-string clamp. After completion of a purse-string suture, a Kelly clamp is applied just proximal to the purse-string clamp and the duodenum is transected between the two clamps. An anvil is inserted into the duodenal stump, and a purse-string suture is tied to fix the anvil.

The appropriate proximal resection margin is determined by directly observing the clip through the gastrostomy, and the greater curvature side is partially transected with a linear stapler. The shaft of a circular stapler is introduced into the stomach through the gastrotomy, then the shaft is rotated toward the duodenum and the trocar is advanced to penetrate the corner of the stapling line at the greater curvature.

The trocar is connected to the anvil that has been placed in the duodenum, and the circular stapler is closed and fired, completing the end-to-end gastroduodenostomy by double stapling. After hemostasis of the intraluminal bleeding, the lesser curvature side of the proximal stomach is transected completely using another linear stapler.

This method has several advantages over other methods of Billroth I anastomosis: ((1) it permits the proximal resection margin to be longer than with other methods; ((2) it results in the equal tension on the anterior and posterior walls of the remnant stomach; and ((3) it does not need an additional gastrotomy on the remnant stomach [21].

Extracorporeal End-to-Side Posterior Wall Method

The distal resection and anvil insertion performed in the extracorporeal end-to-side posterior wall method are the same as in the extracorporeal end-to-end modified double stapling method. For proximal resection, the stomach is transected from the greater curvature to the lesser curvature in two steps: (1) The greater curvature side of the planned proximal margin is grasped with two clamps and transected between the two clamps, and (2) the remaining lesser curvature side is transected using a linear stapler. After the specimen is removed, the shaft of a circular stapler is introduced into the stomach through the gastrostomy, which was previously clamped. The trocar is advanced to penetrate the posterior wall of the remnant stomach. The circular stapler is closed and fired, completing the end-to-side gastroduodenostomy. Finally, the gastrotomy is closed using another linear stapler [22].

Intracorporeal Delta-Shaped Method

The intracorporeal Billroth I method has gained popularity since Kanaya et al. reported the first delta-shaped anastomosis [23]. Delta-shaped anastomosis is a functional end-to-end gastroduodenostomy technique performed using linear staplers, and it offers technical simplicity, wider lumen anastomosis, and a better cosmesis in comparison to the extracorporeal Billroth I methods, and a good surgical field even in obese patients. However, it requires sufficient length of duodenal stump and remnant stomach, so is not recommended when the tumor is located above the angle of the stomach or very close to the pylorus.

After mobilization of the gastroduodenum, a 60-mm linear stapler is introduced through the

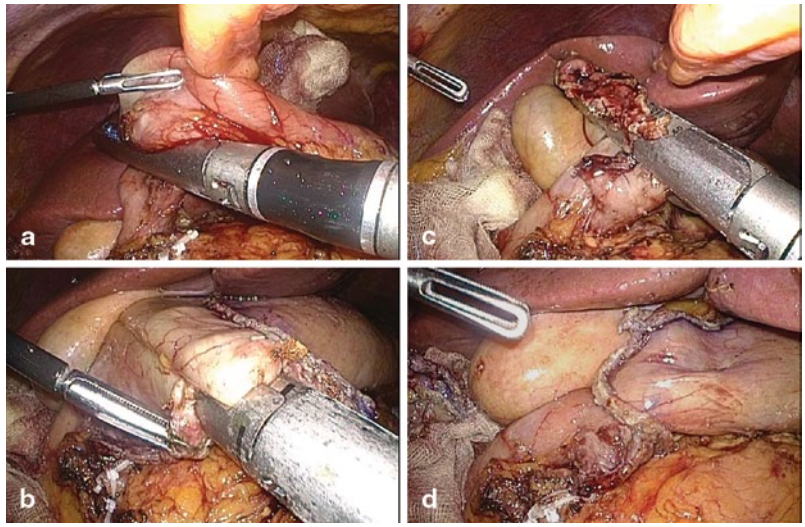

Fig. 15.7 Intracorporeal delta-shaped Billroth I anastomosis. **a** Posteroanterior transection of the duodenum just below the pylorus. **b** Side-to-side gastroduodenostomy. **c** Closure of the entry hole using a 60-mm linear stapler. **d** View after the anastomosis

left lower 12-mm trocar and the duodenal bulb is transected just below the pylorus. The direction of the stapling is more vertical (posteroanterior direction) than the conventional mesenteroantimesenteric direction, resulting in a favorable blood supply and the appropriate angle for the anastomosis (Fig. 15.7a).

After proximal transection of the stomach with several linear staplers, the specimen is removed from the abdominal cavity through the extended umbilical wound. Entry holes are made on the tip of the greater curvature side of the remnant stomach and on the posterior tip of the duodenal stump using laparoscopic electrocautery or a harmonic scalpel. The cartilage jaw of a 45-mm linear stapler is inserted into the stomach and the remnant stomach is rotated to the posterior wall side. The jaw of the stapler is inserted into the duodenal stump and the duodenum is also rotated toward the posterosuperior wall to form a side-to-side (posteroposterior) gastroduodenostomy (Fig. 15.7b). After firing the stapler and hemostasis, the common entry hole is closed by one or two 60-mm linear staplers (Fig. 15.7c, d). Transient approximation of the entry hole using stay sutures can be helpful for making an aligned closure of the common entry hole.

Other Intracorporeal Billroth I Methods

Several intracorporeal Billroth I methods have been introduced that use circular staplers [24–26]. However, these techniques are not preferred over delta-shaped anastomosis because of the technical difficulty in the intracorporeal purse-string suture and long-operation time caused by the extracorporeal processes.

Reconstruction by Gastrojejunostomy After Laparoscopic Distal Gastrectomy

Intracorporeal Billroth II/Uncut Roux-en-Y Method

After radical lymphadenectomy and confirmation of a negative resection margin on the frozen section biopsy, a 15–20 cm jejunal loop from the

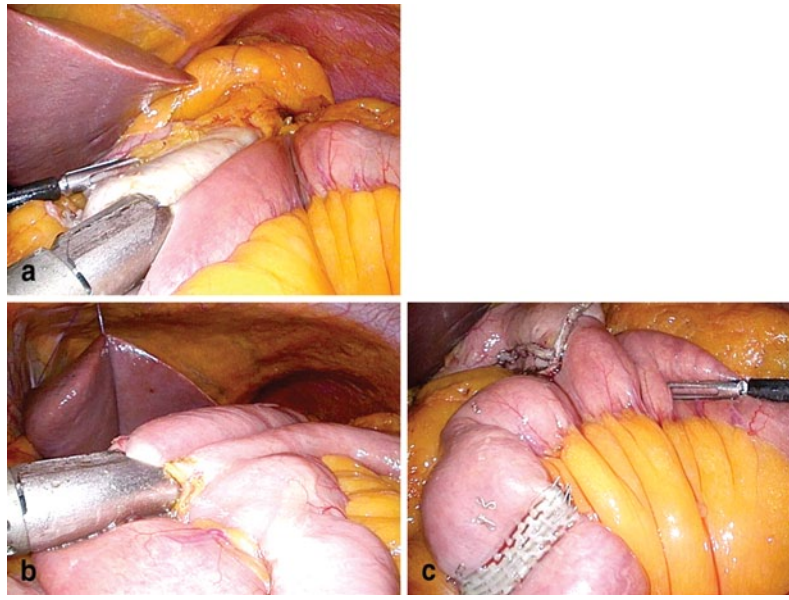

Fig. 15.8 Intracorporeal uncut Roux-en-Y gastrojejunostomy. **a** antiperistaltic side-to-side gastrojejunostomy using a 60-mm linear stapler. **b** Side-to-side jejunojejunostomy using a 60-mm linear stapler. **c** View after uncut procedure on the afferent loop using a 45-mm knifeless linear stapler

ligamentum of Treitz is brought up to the remnant stomach with atraumatic forceps and the jejunal loop is laid besides the remnant stomach in the antiperistaltic direction to examine any tension in the mesentery.

Entry holes are made on the tip of the greater curvature side of the remnant stomach and on the antimesenteric surface of the jejunum using laparoscopic electrocautery or a harmonic scalpel. A 60-mm linear stapler is introduced through the right lower port. The cartilage jaw of the staplers is inserted into the jejunum and the anvil jaw is then inserted into the stomach. The stapler is fired to complete the gastrojejunostomy (Fig. 15.8a). After hemostasis, the common entry hole is closed with another linear stapler or a running suture with an absorbable thread.

Next, in the same manner, a side-to-side jejunojenjunostomy is made in the efferent loop, 25 cm distal from the gastrojejunostomy (Fig. 15.8b). Small entry holes are made on the antimesenteric wall of the afferent and efferent loops and, a linear stapler is introduced into the lumens and fired to create an anastomosis. The common entry hole is closed with another linear stapler or a running suture with an absorbable thread.

To perform the uncut Roux-en-Y gastrojejunostomy, an uncut procedure is added to the conventional Billroth II method. A small opening is made on the mesentery of the afferent loop and a knifeless linear stapler is introduced and fired on the afferent loop between the gastrojejunostomy and jejunojejunostomy (Fig. 15.8c).

Intracorporeal Roux-en-Y Method

A 15–20 cm jejunal loop from the ligament of Treitz is divided with a linear stapler and the jejunal limb is brought cephalad to the remnant stomach. An entry hole can be made on the antimesenteric side of the jejunal limb, 5 cm distal to the cut end, for an isoperistaltic gastrojejunostomy or on the tip of the jejunal limb for a retroperistaltic gastrojejunostomy. The remaining procedures of the gastrojejunostomy and jejunojenjunostomy are the same as for the intracorporeal Billroth II method.

Reconstruction by Roux-en-Y Esophagojejunostomy After Laparoscopic Total Gastrectomy

Laparoscopic esophagojejunostomy is the most critical and technically challenging step in laparoscopic total gastrectomy. Various methods for esophagojejunostomy have been introduced, but no standard protocol exists.

Laparoscopic methods for reconstruction after laparoscopic total gastrectomy are classified into extracorporeal and intracorporeal anastomosis, and further classified into side-to-side anastomosis using linear staplers and end-to-side anastomosis using circular staplers according to the type of esophagojejunostomy.

Extracorporeal Roux-en-Y Method

After completing the lymph node dissection for total gastrectomy and duodenal transection, a 4–5 cm length of vertical mini-laparotomy is made on the epigastrium of the abdomen. The specimen is retrieved and the esophagus is clamped using a purse-string clamp. After the completion of a purse-string suture, a Wertheim clamp is applied just distal to the purse-string clamp, and the esophagus is transected between the two clamps. An anvil is inserted into the esophageal stump, and a purse-string suture is tied to fix the anvil.

A suitable portion of the jejunum is transected and the circular stapler is introduced into the Roux limb via a mini-laparotomy. The trocar is advanced to penetrate the jejunum and is connected to the anvil in the esophagus. The circular stapler is closed and fired to complete the end-to-side esophagojejunostomy. After removal of the instrument, the jejunal stump is transected with a linear stapler.

A jejunojejunostomy is made 40 cm distal from the esophagojejunostomy and the mesenteric defect is closed with continuous or interrupted sutures.

Intracorporeal Side-to-Side Aanastomosis Using a Linear Stapler

Intracorporeal side-to-side anastomosis using a linear stapler requires a sufficient length of esophagus to be freed from the crus before the esophageal transection. For the side-to-side esophagojejunostomy, the remnant esophageal stump should be at least 50 mm long to apply the linear stapler. The esophagus is then transected intracorporeally, just proximal to the gastroesophageal junction, using a linear stapler.

The transverse colon and greater omentum are moved cephalad using atraumatic forceps to enable the ligament of Treitz to be identified. A suitable portion of the jejunum is transected by a linear stapler and the Roux limb is brought up to the remnant esophagus in an antecolic fashion.

There are two side-to-side styles of esophagojejunostomy including a semi-loop and an overlap configuration. For a semi-loop configuration an entry hole is made on the tip of the Roux limb and on the esophageal stump. For an overlap configuration, an entry hole is made on the antimesenteric side of the Roux limb, 10 cm distal to the cut end, and on the right tip of the esophageal stump. Careful exposure of the esophageal mucosa is required to avoid creating a false lumen in the submucosal plane.

A 45-mm linear stapler is introduced through the umbilical port and the jaws of the linear stapler are inserted into the Roux limb and the esophagus step-by-step. The stapler is fired to create the anastomosis and the internal staple line is checked to ensure hemostasis. Finally the common entry hole is closed with another linear stapler or an absorbable suture. The Roux-en-Y reconstruction is completed by performing a jejunojejunostomy, which can be done intracorporeally in a side-to-side fashion by a linear stapler.

Intracorporeal End-to-Side Anastomosis Using a Circular Stapler

After radical lymphadenectomy, the laparoscopic purse-string suture instrument (Lab Jack; Greenmate Biotec, Seoul, Korea) is introduced into the

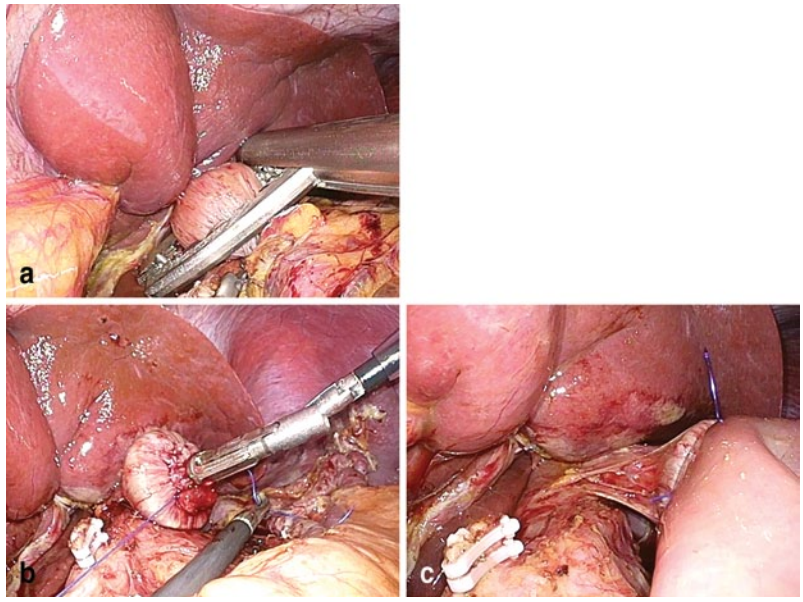

Fig. 15.9 Intracorporeal esophagojejunostomy using a circular stapler. **a** Application of the laparoscopic purse-string suture instrument to the esophagus. **b** Insertion of the anvil head and tying the purse-string suture. **c** Intracorporeal end-to-side esophagojejunostomy

abdominal cavity through the left lower 12-mm trocar. The jaws of the purse-string suture instrument are opened, applied to the distal esophagus, and then closed (Fig. 15.9a). A double-ended suture with straight needles is passed though the instrument, an endoscopic bulldog clamp is placed distal to the purse-string clamp and the esophagus is then transected between the two clamps.

The left lower port is extended to a length of 3–4 cm, and a wound protector is applied. The specimen is removed from the abdominal cavity via mini-laparotomy. The anvil head of the circular stapler is placed in the abdominal cavity and the pneumoperitoneum is reestablished when the resection margin is negative for tumor on frozen section biopsy. The anvil head is inserted into the esophageal stump intracorporeally using a laparoscopic anvil grasper, and the purse-string suture is tied laparoscopically (Fig. 15.9b). An additional pre-tied loop is subsequently placed and tightened just proximal to the purse-string suture.

After the jejunum is retrieved via a mini-laparotomy, the jejunum is transected 20 cm from the ligament of Treitz and a circular stapler is introduced into the Roux limb. An end-to-side esophagojejunostomy is performed intracorporeally, then the circular stapler is withdrawn and the jejunal stump is closed with a 60-mm linear stapler (Fig. 15.9c).

A side-to-side jejunojejunostomy is performed extracorporeally using linear staplers and the jejunojejunal mesenteric defect is sutured.

Intracorporeal End-to-Side Anastomosis Using a Transorally Inserted Anvil

There is a commercially available, ready-to-use anvil delivery device (OrVil^{TM}; covidien, Mansfield, MA, USA) that is designed to insert the anvil transorally into the esophagus, similar to inserting an orogastric tube.

After transection of the esophagus with a linear stapler, the OrVil^{TM} tube is introduced transorally. When the tube's tip reaches the esophageal stump, a small hole is created in the esophageal stump and the tube is then extracted until the anvil head reaches the esophageal stump. The

tube is easily disconnected from the anvil by cutting the thread, and is removed from the abdominal cavity.

A 4 cm vertical mini-laparotomy is then made on the epigastrium, approximately at the area closest to the ligament of Treitz and the subsequent Roux-en-Y reconstruction is same as for the intracorporeal end-to-side anastomosis using a circular stapler.

Reconstruction After Laparoscopic Proximal Gastrectomy

The incidence of proximal gastric cancer has recently increased, and proximal gastrectomy is widely accepted as a function-preserving surgery for patients in the early stage of proximal cancer. Despite functional benefits such as improved nutrition and preventing anemia, proximal gastrectomy has not gained in popularity, mainly due to the high incidence of postoperative complications, such as reflux esophagitis and anastomotic stricture. Reconstructions such as jejunal interposition and double-tract reconstruction may prevent severe reflux after proximal gastrectomy and these procedures can also be performed laparoscopically.

End-to-End Esophagogastrostomy

Direct esophagogastrostomy used to be widely performed because of its simplicity; however it causes severe gastroesophageal reflux in some patients. Several methods have been developed to replace direct esophagogastrostomy including antireflux procedure, side-to-side anastomosis, and preservation of the lower esophageal sphincter [27–29].

To perform an extracorporeal esophagogastrostomy, a circular stapler is introduced through a gastrostomy located on the anterior wall of the remnant stomach via a mini-laparotomy. After completion of the anastomosis the entry hole is closed using a linear stapler [29–31].

Uyama et al. introduced a laparoscopic overlap method for a side-to-side esophagogastrostomy that uses a linear stapler and, involves attaching the posterior aspect of the esophagus to the anterior wall of the gastric remnant [27].

Double-Tract Reconstruction

After a pure-string suture of the esophagus and completion of a lymphadenectomy, the specimen is retrieved via a transverse mini-laparotomy that is extended from the left lower trocar site. The proximal stomach is transected using a linear stapler after the distal resection margin has been ensured and the gastroepiploic arcade has been trimmed. A single stitch is placed on the remnant stomach and the stomach is returned inside the abdominal cavity.

The anvil head of the circular stapler is placed in the abdominal cavity and the pneumoperitoneum is reestablished. The anvil head is inserted into the esophageal stump intracorporeally using a laparoscopic anvil clamp, and the purse-string suture is tied laparoscopically. After the jejunum is retrieved via the mini-laparotomy, the jejunum is transected and a circular stapler is introduced into the Roux limb. An end-to-side esophagojejunostomy is performed intracorporeally, then the circular stapler is withdrawn and the jejunal stump is closed with a linear stapler.

A side-to-side gastrojejunostomy 15 cm distal from the esophagojejunostomy is then made in an extracorporeal fashion using a linear stapler. A liner stapler is introduced cephalad into the stomach and the Roux limb and fired, before the common entry hole is closed with another stapler. In the same manner, a side-to-side jejunojejunostomy is made 20 cm distal from the gastrojejunostomy using linear staplers. The jejunojejunal mesenteric defect is sutured to prevent an internal herniation of the small bowel [32, 33].

Jejunal Interposition

The laparoscopic jejunal interposition is relatively complex in comparison to the double-tract reconstruction. To perform a jejunal interposition

a pedicled jejunal limb and three anastomoses including an esophagostomy, a jejunogastrostomy, and a jejunojejunostomy, must be created. Thus, there are very few reports that have described a laparoscopic proximal gastrectomy with jejunal interposition, despite its favorable outcomes for preventing postoperative reflux [33–35].

Recently, a modified laparoscopic method was introduced by Nomura et al. [33]. After double-tract reconstruction, the jejunal interposition was completed by a simple closure of the jejunum on the caudal side of jejunogastrostomy, performed with a knifeless linear stapler.

Reconstruction After Laparoscopic Pylorus-Preserving Gastrectomy

Pylorus-preserving gastrectomy with radical lymphadenectomy has been used to treat patients with early gastric cancer. It preserves pyloric function and has several advantages over subtotal gastrectomy, including reduced risk of dumping syndrome and a lower incidence of disturbed bowel habits.

Laparoscopy-assisted pylorus-preserving gastrectomy has been used as a minimally invasive function-preserving surgery and had better outcomes than laparoscopy-assisted distal gastrectomy in terms of nutrition and incidence of gallstones [36].

Extracorporeal Gastrogastrostomy

For extracorporeal gastrogastrostomy, a 5 cm midline incision is made on the epigastrium. The distal part of the stomach is resected while retaining a 3 cm-long pyloric cuff. The proximal portion of the stomach is then transected with an Allen clamp on the greater curvature and then using a 100-mm linear cutter on the lesser curvature side.

A single-layer continuous interlocking gastogastric anastomosis is performed using 3-0 vicryl. The stomach is placed back into the abdominal cavity [37].

Intracorporeal Gastrogastrostomy Using Linear Staplers

A totally laparoscopic pylorus-preserving gastrectomy has been introduced [38, 39]. The anastomosis is formed intracorporeally using a 60-mm linear stapler and the common entry hole is closed with another stapler. This technique is very similar to that used for the delta-shaped anastomosis technique.

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16 Robotic Methods of Resection and Reconstruction for Subtotal and Total Gastrectomy with D2 Lymphadenectomy

Taeil Son and Woo Jin Hyung

Introduction

Minimally invasive surgery (MIS) for gastric cancer has seen many advances over the past few years, and offers benefits of less blood loss, decreased pain, earlier restoration of bowel motility, and shorter hospital stay than conventional open surgery [1, 2]. Nevertheless, while most consider laparoscopic gastrectomy a safe and feasible modality for managing gastric cancer, lymphadenectomy for gastric cancer remains a technically demanding procedure for most surgeons [3–6]. Meanwhile, despite a lack of evidence on proper indication for MIS, including robotic surgery, indications for MIS in treating gastric cancer have expanded from early gastric cancer to advanced cancers, in which performance of D2 lymph node (LN) dissection is essential. Notwithstanding, a few experienced surgeons at large volume centers have demonstrated the feasibility of D2 LN dissection during radical gastrectomy [3, 7–10]. Meanwhile, to overcome the technical limitations of conventional laparoscopic surgery and to carry out more precise and refined procedures, the use of robotic surgical systems to perform gastrectomy has recently increased.

Operative Indications

To date, robotic gastrectomy has been performed in gastric cancer patients indicated for a laparoscopic procedure [11]. Currently, throughout the East, minimally invasive gastrectomy is widely performed for early gastric cancer: indications for minimally invasive surgery of gastric cancer differ between Eastern and Western countries [12, 13]. Robotic gastrectomy with limited LN dissection (D1 or D1+) is indicated for cT1N0M0 cancer, which does not meet the criteria for endoscopic treatment, such as endoscopic mucosal resection or endoscopic submucosal dissection. Robotic gastrectomy with extended LN dissection (D2) is indicated for cT1N1M0, cT2N0M0, cT2N1M0, cT3N0M0, and cT3N1M0. Generally, serosa-involved (cT4a) and more advanced gastric cancers, as well as patients unable to tolerate pneumoperitoneum, are not indicated for this type of procedure. Extensive LN metastasis and bulky tumors are also contraindicated for robotic surgery. Nonetheless, in practice, indications can vary depending on a surgeon's experience and expertise.

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Preoperative Evaluation and Preparation

Preoperative evaluation of patients indicated for robotic surgery includes history taking, physical examination, and comprehensive work-up of tumor characteristics consisting of tumor depth, location, nodal status, and distant metastasis. To plan a surgical procedure, esophagogastroduodenoscopy, endoscopic ultrasound, and computed tomography (CT) scan of the abdomen are routinely required. Chest CT scan and positron emission tomography (PET) combined with CT are also recommended according to some guidelines [14]. In cases of small, nonpalpable early tumors, tumor localization via preoperative endoscopic clipping or intraoperative endoscopic guidance is required to determine proximal resection line [15–17].

Operative Technique

Operating Room Setup and Patient Positioning

Preferably, patients are to be placed in the supine position with both arms tucked to the patient's sides. The operating table can then be tilted to a reverse Trendelenburg position of 15°. To complete setup of the operating room, the robot surgical cart should be positioned near the patient's head parallel to the operating table, with an assistant surgeon on the patient's left side, and a scrub nurse on the patient's right side.

Port Placement, Docking, and Instrumentation

A total of five trocars, including an assistant's port, are used in standard subtotal and total gastrectomy (Fig. 16.1a). A 12-mm trocar is used for camera installation just below the umbilicus. The No. 1 arm, which mainly holds Maryland curved bipolar forceps, should be placed along the patient's anterior axillary line. The No. 2 arm is to be placed along the patient's right midclavicular line, just caudal to the level of duodenum, to facilitate suprapancreatic dissection; this position facilitates the use of energy devices (ultrasonic shears or monopolar scissors) and Cadiere forceps, which can be interchanged between the No. 2 and 3 arms. A 12-mm assistant's port can be placed along the patient's left midclavicular line at an imaginary point 2–3 cm caudal between the camera port and the No. 1 arm (Fig. 16.1b). Thereafter, the surgical cart can be brought to the operating table, over the head of patient, to dock the robotic arms.

Liver Retraction and Intraoperative Tumor Localization

Liver retraction is critical for clear visualization of the operative field. There are various liver retraction methods for upper gastrointestinal surgery: an example is the so-called liver suspension with suture-gauze technique (Fig. 16.2a) [18–20]. Regardless of the method chosen, the area around the hepatoduodenal ligament, lesser omentum and gastroesophageal junction must be exposed. In cases of distal subtotal gastrectomy, intraabdominal tumor localization is required before docking of the robotic arms [17]. To do so, metallic surgical clips are roughly placed along the greater and lesser curvatures of the stomach to demarcate the location of gastric transection. The ultimate resection line should be determined after comparing the locations between the surgical clips and intragastric hemoclips placed around the lesion during preoperative endoscopy (Fig. 16.2b).

D2 Lymphadenectomy During Distal Subtotal Gastrectomy

Mobilization of the Greater Omentum

To divide the gastrocolic ligament and retrieve LN stations No. 4sb and 4d, surgeons should first retract the stomach by pulling the omentum in the direction of the patient's head via Cadiere forceps placed in the No. 3 arm. With the use of

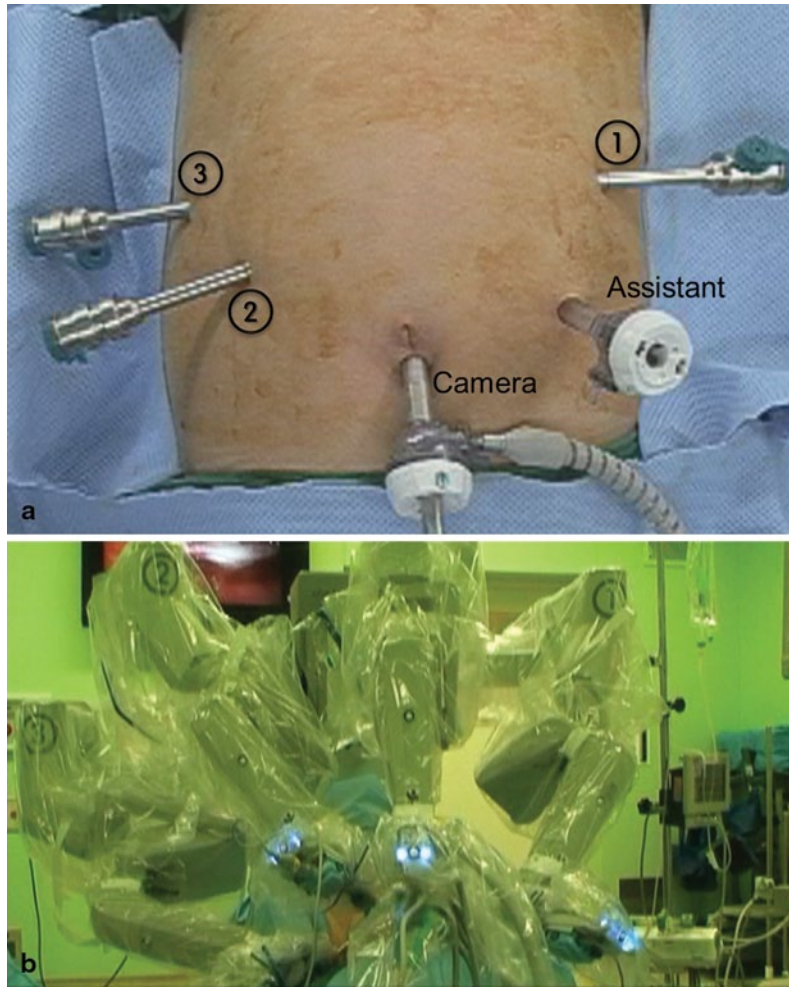

Fig. 16.1 **a** Port placement for robotic gastrectomy. **b** Docked robot arms

the energy devices (ultrasonic shears or monopolar scissors) in the No. 2 arm, the lesser sac can be opened by dividing the gastrocolic ligament along the mid-transverse colon (Fig. 16.3a). The greater omentum can then be further divided toward the lower pole of the spleen. To facilitate optimal exposure of the lesser sac, proper repositioning of the omentum via the Cadiere forceps and counter traction of the transverse colon via the Maryland forceps in the No. 1 arm is essential. By this method, the left gastroepiploic vessels can be easily identified and ligated at the root using clips (Fig. 16.3b). D2 LN dissection usually comprises total omentectomy; however, partial omentectomy is an option in cases of cT1 or cT2 tumors. After clearing LN station No. 4sb, soft tissue along the greater curvature of the stomach from the imaginary proximal resection line is to be cleared to the point just distal to the short gastric vessel to complete left side LN dissection.

Infrapyloric Dissection

To complete infrapyloric dissection, relevant vascular anatomy around the head of the pancreas and duodenum should be well understood. Facilitated by the No. 3 arm, the distal stomach can be mobilized anteriorly from the head of the pancreas. LN bearing soft tissues, comprising station No. 6, which is bordered by the right gastroepiploic vein, the anterior supe-

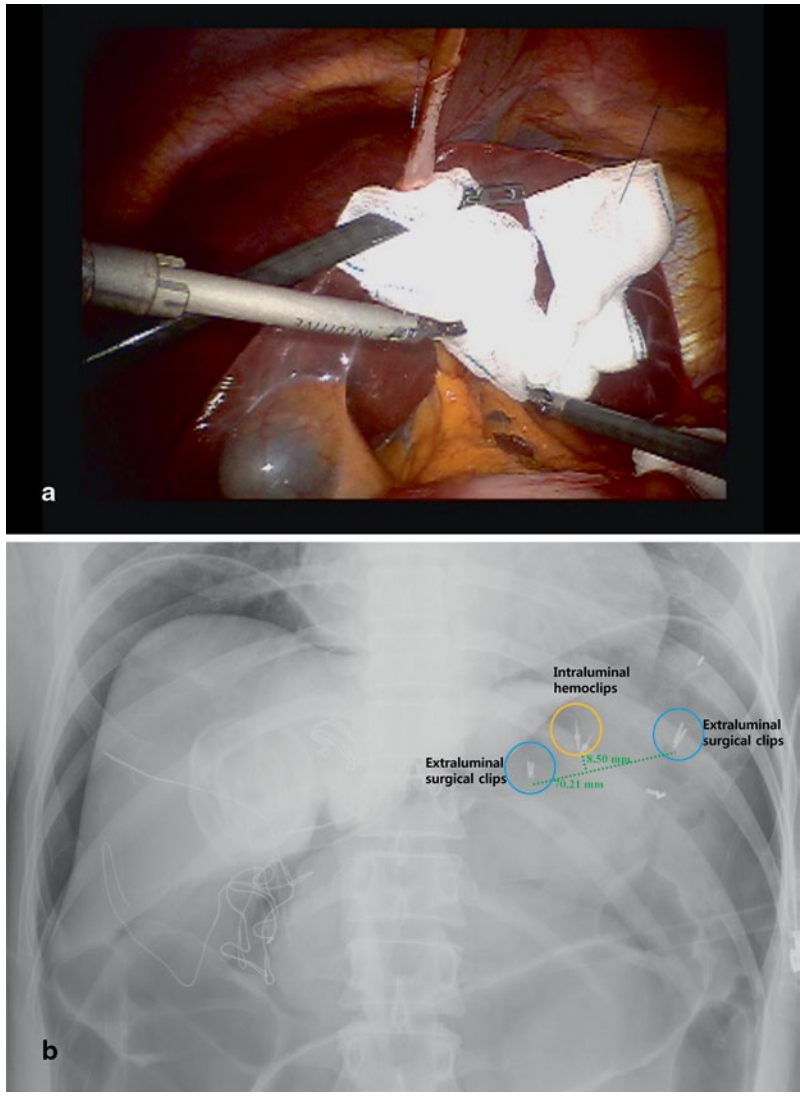

Fig. 16.2 **a** Liver retraction with a suture-gauze technique **b** Intraoperative X-ray for measuring the distance between surgical clips and intraluminal hemoclips. In this case, total gastrectomy was required

rior pancreaticoduodenal vein (ASPDV), and the middle colic vein, should be accurately identified and dissected. Ligation of the right gastroepiploic vein is to be completed at the point where it joins the ASPDV (Fig. 16.3c). Subsequently, the right gastroepiploic artery (RGEA) can be identified at the end of the gastroduodenal artery (GDA) and ligated at the root thereof (Fig. 16.3d). Continued dissection will allow for identification of the infrapyloric artery in most cases, which should be isolated and ligated. Thereafter, the attachment between the posterior wall of the duodenum and the pancreas can be cleared up to the root of the GDA.

Suprapyloric Dissection and Duodenal Transection

To prevent undesired injury to the common hepatic artery (CHA) or pancreatic parenchyma during suprapyloric dissection, 4×4 gauze

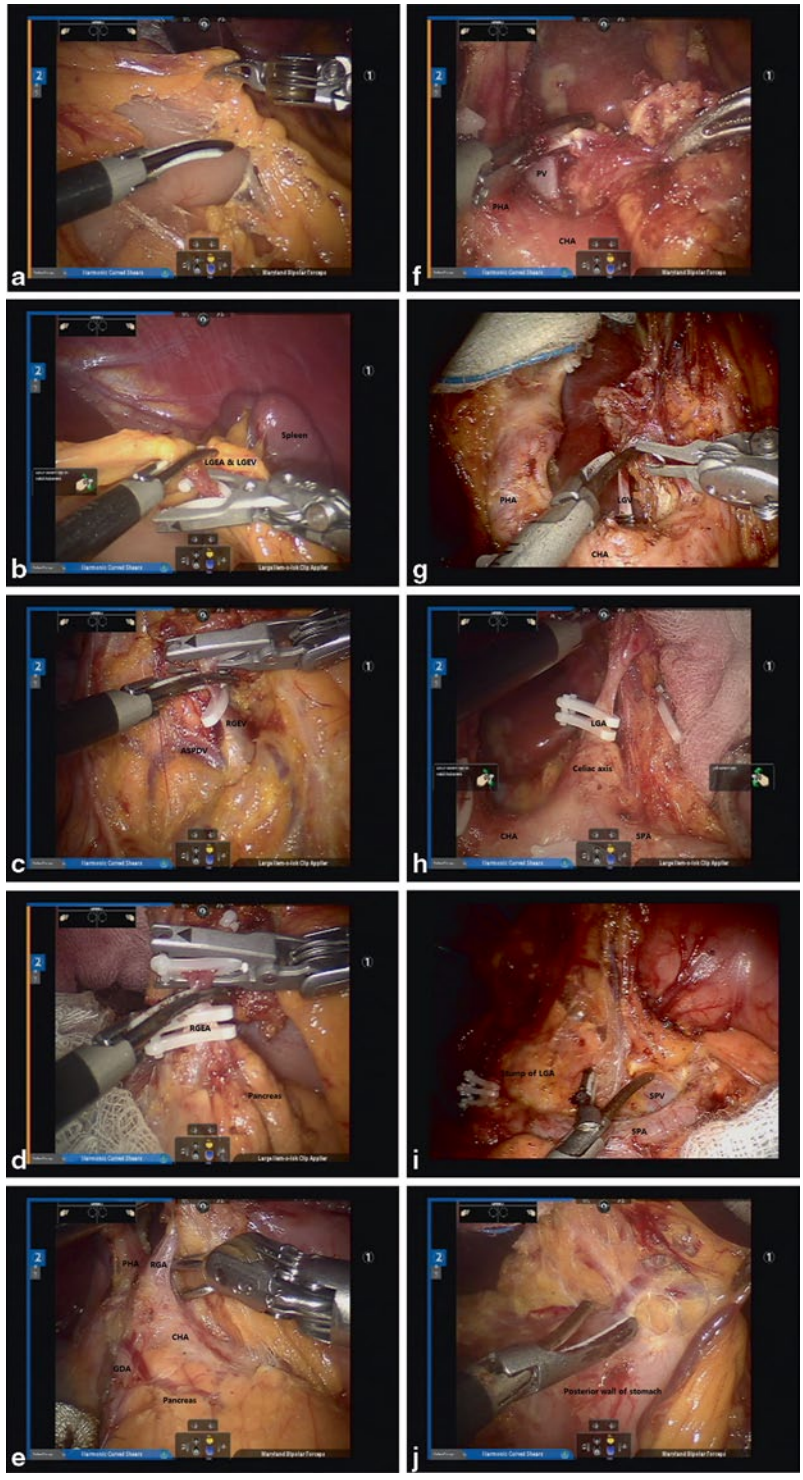

Fig. 16.3 **a** Division of the gastrocolic ligament. **b** Ligation of the Left gastroepiploic artery (LGEA) and Left gastroepiploic vein (LGEV). **c** Exposure of the Right gastroepiploic vein (RGEV) and ASPDV and ligation of the RGEV. **d** Isolation and ligation of the RGEA. **e** Exposure and ligation of the RGA. **f** Dissection of the hepatoduodenal ligament. **g** Isolation and ligation of the Left gastric vein (LGV). **h** Isolation and ligation of the LGA. **i** Dissection along the SPA. **j** Dissection of the lesser omentum along the lesser curvature

should be inserted in the space between the posterior duodenum and the head of the pancreas. Soft tissues can then be cleared just above the pylorus to a distal point about 2 cm thereto to make a path for a linear stapler. Then, the duodenum can be transected by the assistant surgeon using the linear stapler.

Suprapancreatic Dissection

After dividing the duodenum, the right gastric vessels are to be retracted to the patient's left to generate proper tension on the vessels. Dissection is then started from the right lateral surface of the proper hepatic artery (PHA), possibly led by the GDA, which was previously exposed. The right gastric artery can then be identified and ligated at the origin (Fig. 16.3e). This completes the retrieval of LN station No. 5. By dissecting anteriorly and medially to the PHA, LN station No. 12a can be cleared. Complete dissection of LN station No. 12a can be ensured by exposing the portal vein (PV) (Fig. 16.3f). At this time, the assistant surgeon could retract the CHA inferiorly or the PHA toward the patient's right to facilitate better exposure. Thereafter, the dissection is to continue around the CHA for the retrieval of LN station No. 8a. The left gastric artery (LGA) can then be gently retracted to the anterior abdominal wall to expose the lesser curvature. Next, the left gastric vein should be identified and securely ligated at the point where it drains into the PV or splenic vein (SPV) (Fig. 16.3g). Continuing the retroperitoneal dissection, remove the soft tissues along the LGA, celiac axis, and splenic vessels, which are designated as LN station Nos. 7, 9, and 11p, respectively. Once exposed, the root of the LGA can be ligated (Fig. 16.3h). Continued dissection of soft tissues toward the celiac trunk will allow for retrieval of LN station No. 9. Next, LN station No. 11p bearing soft tissues can be removed from the superior border of the pancreas and splenic artery (SPA) toward the middle of the SPA. Typically, a posterior gastric artery is present and can act as a landmark of the dissection border. To complete dissection of LN station No. 11p, thorough exposure of the anterior and superior borders of the SPA and SPV is generally suggested (Fig. 16.3i).

Lesser Omentum Dissection and Gastric Transection

Next, the lesser omentum along the lesser curvature from the esophageal crus down to the gastric resection line can be dissected and cleared (Fig. 16.3j). Truncal vagotomy is performed at this time by dividing the vagus nerves, which runs anteriorly and posteriorly around the esophagus. This completes dissection of LN station No. 1. After the stomach is fully mobilized, by clearing the area around LN station No. 3, it can be transected by the assistant surgeon using two or three linear staplers, completing the D2 lymphadenectomy for distal subtotal gastrectomy.

D2 Lymphadenectomy During Total Gastrectomy

Total gastrectomy with D2 LN dissection involves LN removal around distal splenic vessels (LN station No. 11d) and the splenic hilum (LN station No. 10) with or without splenectomy. To prevent increased morbidity related to the splenectomy, spleen-preserving total gastrectomy with D2 LN dissection is possible. However, splenic hilar dissection for the purpose of spleen-preservation is a highly-demanding procedure, although experienced surgeons can perform it successfully. Notwithstanding, use of magnified 3D views from the robotic system and the articulated movements of the robotic arms allows for this complex and difficult procedure to be more readily performed. The detailed procedures thereof include dissection of LNs around the distal splenic vessels and the splenic hilum. To begin, the short gastric vessels are divided after ligating the left gastroepiploic vessels. After division of the short gastric vessels at their roots, the esophagophrenic ligament is divided for mobilization of the esophagus. Subsequently, branches of the splenic vessels can be identified and ligated from the lower pole toward the upper pole of the spleen and from the splenic hilum toward proximal part of the splenic vessels (Fig. 16.4a and b).

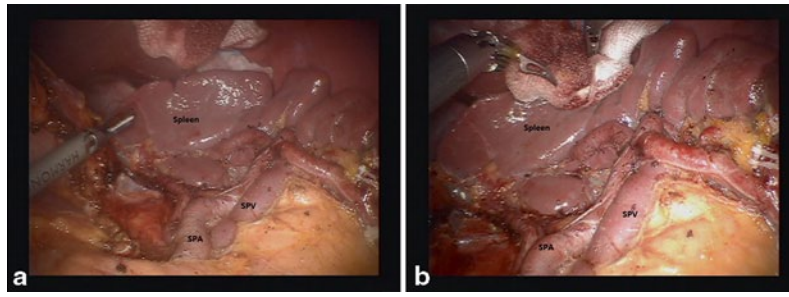

Fig. 16.4 **a** Complete dissection along the splenic artery and hilum during spleen-preserving total gastrectomy. **b** Completion of splenic hilar dissection

Reconstructions

Depending on the location of tumors or the size of remnant stomach after distal subtotal gastrectomy, bowel continuity can be restored by gastroduodenostomy (Billroth I) and gastrojejunostomy (Billroth II). Roux-en-Y gastrojejunostomy is also worth considering. In instances of total gastrectomy, Roux-en-Y esophagojejunostomy is routinely performed. Intracorporeal stapled anastomosis can be used for totally robotic gastrectomy. Robotic sutured anastomosis is also feasible [21]. Up to now, however, stapling has been carried out by the assistant surgeon during robotic surgery. There are several reconstruction methods used during laparoscopic distal subtotal or total gastrectomy that can also be applied for robotic surgery [22–26]. Herein, a few of these intracorporeal anastomosis techniques after robotic distal subtotal and total gastrectomy are described.

Intracorporeal Gastroduodenostomy (Billroth I)

Intracorporeal gastroduodenostomy is the first option for restoration of intestinal continuity after distal subtotal gastrectomy, whenever indicated [27]. Using linear staplers, surgeon can perform gastroduodenostomy also known as delta-shaped anastomosis [25, 27]. To do so, the duodenum should be transected from the posterior to anterior wall using a 45-mm linear stapler. After gastric transection, a small entry hole in the remnant stomach is created along the resection line of the greater curvature. The medial edge of the duodenal stump can also be opened to create an entry hole. Using a 45-mm linear stapler, a common channel is formed between the posterior wall of the stomach and the posterior wall of the duodenum after which the entry hole can be closed by another two 45-mm linear staplers. Unlike conventional delta-shaped anastomosis, there are some modifications. Some surgeons prefer to remove the previous stapling line of the duodenum, when closing the entry hole. During the procedure, linear staplers can be inserted and used via the assistant port.

Intracorporeal Gastrojejunostomy (Billroth II)

When gastroduodenostomy is not indicated after distal subtotal gastrectomy, intracorporeal gastrojejunostomy can be performed by antecolic, isoperistaltic loop gastrojejunostomy [22, 27]. After complete resection, the remnant stomach is measured and the jejunal loop is mobilized in order to make entry holes for a linear stapler. Thereafter, an entry hole in the stomach is created at the greater curvature about 6 cm apart from the previous transection line. Sometimes a short gastric artery may need to be sacrificed. Then, an entry hole in the loop of the jejunum 15–20 cm away from the ligament of Treitz is created at the antimesenteric border. A 60-mm-sized linear stapler can then be introduced from an assistant port on the left side and accommodated in the stomach and the jejunum one by one. The jejunum should be gently brought up around the hiatus and then, inserted gently using the robotic arms. After side-to-side anastomosis is performed, the

No. 2 arm of the robot needs to be undocked and an 8-mm port should be replaced with a 12-mm trocar to facilitate use of a linear stapler for closure of the entry hole. Using a 60-mm linear stapler on the right side, the common enterotomy can be closed. The entry hole may also be closed by a robotic hand-sewn technique.

Intracorporeal Roux-en-Y Esophagojejunostomy

Intracorporeal antecolic Roux-en-Y esophagojejunostomy using linear staplers is routinely performed after total gastrectomy. For Roux-en-Y esophagojejunostomy, abdominal esophagus is transected from the ventral to dorsal side with a 45-mm linear stapler by rotating the esophagus counter clockwise. An entry hole in the esophagus is then made at the dorsal edge of the resection line. After the jejunum is brought up to the anastomosis site, an entry hole in the antimesenteric border of the jejunum is created at point 15–20 cm distal to the Treitz ligament where no tension is present. A 45-mm linear stapler can then be inserted into the holes, facilitating side-to-side anastomosis. The common entry hole can subsequently be closed with a 45-mm stapler or by suture. The afferent loop of the jejunum is then transected using a stapler. Jejunojejunostomy is finally made at a point 45–50 cm distal to the esophagojejunostomy using linear staplers. Mesenteric defect can be closed with running sutures by a robotic hand-sewn technique. When transecting the esophagus, closing the common entry hole, and creating the jejunojejunostomy, the No. 2 arm should be undocked and replaced with a 12-mm trocar to permit use of the staplers.

Postoperative Care

Postoperative management includes appropriate fluid maintenance, pain control, and resumption of oral intake. The following is a typical postoperative management strategy: Return of gastrointestinal function is usually expected in 3–5 days in patients without complication. If tolerable, water is given from postoperative day (POD) 2; the next day a liquid diet is started and advanced to a soft diet on POD 4 [28]. If tolerable and there is no evidence of complication, the patient is recommended for discharge on POD 5. The median length of postoperative hospital stay is 5 days if there are no postoperative complications [28].

Complications

The complication rates for the procedures above are similar to that of laparoscopic gastrectomy [11, 22]. Reported complications consist of wound complication, intraabdominal fluid collection or abscess, pancreatitis, pancreatic fistula, ileus, intestinal obstruction, intraluminal bleeding, and anastomosis leakage. Generally, complications after radical gastrectomy are related to extent of LN dissection, and therefore, D2 LN dissection is expected to have more complications than limited LN dissection. Nevertheless, robotic surgery is heralded as reducing surgical complications via thorough and accurate LN dissection. In fact, robotic gastrectomy-related complications are rarely reported. However, care should be taken not to move intraabdominal robotic arms without direct vision.

Results and Outcomes

Many studies have demonstrated the feasibility and safety of robotic gastrectomy for gastric cancer. Nevertheless, the role of robotic surgical systems in gastric cancer treatment is still unclear [11, 29–31]. Compared to conventional laparoscopic surgery, robotic surgical treatment leads to similar short- and long-term results, while it has longer operation times and higher cost. However, allowing for greater precision, robot surgery is expected to facilitate more thorough and accurate LN dissection, which may provide potential survival benefits and staging accuracy. The other reported advantages of robotic surgery compared to conventional laparoscopic gastrectomy are less blood loss and a short learning curve [28, 32–34]. As well, various functions of robotic systems, such as in navigation surgery (Tilepro®)

and in image-guided surgery using near infrared (NIR) fluorescent light, are being investigated [35, 36]. Although results have only been reported for early experience with robotic gastrectomy, robotic-assisted procedures are expected to show more benefits after accumulation of greater experience. As well, investigators suggest that robotic surgery will show more advantages when it is applied to more technically demanding procedures such as far advanced cancer, multiorgan resection and function-preserving gastrectomies [3, 11, 37].

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Managing Early and Late Postoperative Complications Following Gastric Surgery

17

Brian Badgwell, Ryan Day and Thomas Aloia

Introduction

Gastric surgery is complex and is associated with high rates of morbidity, mortality, and hospital readmission. Complications can be divided into early (most often defined as within 30 days of surgery) and late. The majority of early complications after gastric surgery include common surgical morbidities such as anastomotic leakage, wound infections, abscess, bowel obstruction, and the risks of general surgery, such as cardiovascular events, respiratory complications, and venous thrombosis. Postoperative complications can lead to readmission, which is of concern because of the proposed reductions in payments by the Centers for Medicare and Medicaid Services to hospitals with high readmission rates. Readmission rates after gastrectomy are significant, ranging from 10 to 20% within 30 days of surgery. Late complications include not only delayed presentation of early complications but also unique complications of gastrectomy, including the so-called postgastrectomy syndromes. Postgastrectomy syndromes include bile reflux gastritis, dumping syndrome, afferent and efferent limb syndrome, Roux stasis syndrome, and postvagotomy diarrhea. This chapter discusses overall morbidity and mortality rates of patients who have undergone resection for gastric cancer and will describe early and late complications of gastric surgery, with a focus on diagnosis, medical management, and surgical treatment.

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Early Postoperative Complications

Overall Morbidity and Mortality Rates Clinical trials often provide some of the highest quality data on morbidity and mortality rates for surgery. Several prospective trials in gastric cancer contain early postoperative outcomes and have reported fairly consistent morbidity and mortality rates. Many of these randomized trials compared regional and extended lymphadenectomy, although some studies regarded resection of the spleen and the tail of the pancreas as necessary for removing the D2 lymph nodes. The Dutch trial of 711 patients undergoing resection with curative intent reported morbidity and mortality rates of 25 and 4%, respectively, in patients undergoing D1 dissection and 43 and 10% in patients undergoing D2 dissection [1]. The Medical Research Council Gastric Cancer Surgical Trial, in a similar study to the Dutch trial, compared early complications after D1 dissection with those after D2 dissection. Morbidity and mortality rates in the

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Table 17.1 Postoperative morbidity and mortality in clinical trials of surgery for gastric cancer

Trial, year	Morbidity rate (%)	Mortality rate (%)	Anastomotic leakage	Reoperation rate	Length of stay (days)
MRC Gastric Cancer Surgical Trial, 1996[2]	28–46	7–13	11–26%	ND	14
Italian Gastric Cancer Study Group, 1998[3]	21	3	7%	3%	17
Dutch Trial, 1999[1]	25–43	4–10	ND	ND	14–16
MAGIC Trial, 2006[4]	45	6	ND	ND	13

MRC Medical Research Council, *MAGIC* Medical Research Council Adjuvant Gastric Infusional Chemotherapy, *ND* not described

D1 dissection group were 28 and 7%, respectively, compared with morbidity and mortality rates of 46 and 13% in the D2 dissection group [2]. The Italian Gastric Cancer Study Group, in a prospective multicenter trial evaluating complications after pancreas-preserving D2 lymph node dissection, reported a postoperative morbidity rate of 21% and a hospital mortality rate of 3% [3]. Important findings from this study, in addition to the low overall morbidity rate, were variable hospital mortality rates of 1% after subtotal gastrectomy and 7% after total gastrectomy. The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial of perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer included postoperative complications as outcome measures. Morbidity and mortality rates for patients in this trial were 45 and 6%, respectively, and these rates were similar in patients treated with chemotherapy or with surgery alone [4]. Table 17.1 summarizes the overall complication rates for gastrectomy in gastric cancer trials and provides an overview to guide more in-depth discussion of specific complications. In addition, a recent Cochrane review has summarized four randomized clinical trials evaluating the need for abdominal drainage after gastrectomy. This review reported a low 30-day overall mortality rate (1.4%), with no difference in the rate of complications between patients with or without drain placement at surgery [5].

Programmatic databases such as The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database and The Veterans Affairs National Surgical Quality Improvement Program (VA NSQIP) can also provide high-quality data on 30-day morbidity and mortality after gastrectomy for cancer. In a recent study that used the ACS NSQIP participant use file from 2005 through 2010, overall postgastrectomy serious morbidity occurred in 24% of patients and the 30-day mortality rate was 4% [6]. Patients undergoing total gastrectomy had serious morbidity and mortality rates of 29 and 5%, respectively, and patients undergoing partial gastrectomy had serious morbidity and mortality rates of 20 and 3%, respectively (Table 17.2). An older VA NSQIP study of patients undergoing gastrectomy for cancer from 1991 through 1998 reported 30-day morbidity and mortality rates of 33 and 8%, respectively [7].

Surgical Site Infections Superficial, deep, and organ space infections occur in approximately 6, 1, and 7%, respectively, of patients undergoing gastrectomy for cancer, with only slightly higher rates of organ space infection in patients undergoing total gastrectomy than in those undergoing subtotal gastrectomy [6].

Table 17.2 Postoperative 30-day morbidity and mortality rates in patients undergoing total and partial gastrectomy for gastric cancer in ACS NSQIP from 2005 to 2010 [6]

Operation	Serious morbidity (%)	Mortality (%)	Sepsis (%)	Organ space infection (%)	Reoperation rate (%)	Median length of stay (days)
All gastrectomy	24	5	7	7	8	12
Partial gastrectomy	20	3	6	6	6	12
Total gastrectomy	29	5	9	9	10	13

Wound Disruption Wound dehiscence occurs in 1–2 % of patients.

Pulmonary Complications Postoperative pneumonia occurs in about 7 % of patients but can be as high as 12 % in high-risk populations, such as patients receiving care in the United States Department of Veterans Affairs hospital system [6, 7]. Failure to wean from ventilator assistance after 48 h and reintubation occur in 6 % of patients, with higher rates in patients undergoing total gastrectomy.

Bleeding Postoperative hemorrhage or requirement of transfusion of more than 4 units of blood occur in approximately 3 % of patients [7].

Cardiac Complications Cardiac arrest and myocardial infarction occur in 1–3 % of patients.

Deep Vein Thrombosis and Pulmonary Embolism Venous thrombosis occurs in 1–2 % of patients. Pulmonary embolism also occurs in 1 % of patients undergoing partial gastrectomy and in 2 % of patients undergoing total gastrectomy [6].

Urinary Tract Infection Urinary tract infection occurs in up to 6 % of patients.

Reoperation Reoperation is needed and occurs in 6–10 % of patients and occurs more often in patients undergoing total gastrectomy.

Delayed Gastric Emptying Early delayed gastric emptying after subtotal gastrectomy is not infrequent and is likely exacerbated by regional lymph node dissection along the lesser curvature of the stomach with resection of the vagus nerve branches. Medical management includes supplementing the patient's nutrition through total parenteral nutrition or tube feedings and prescribing promotility agents such as metoclopramide and erythromycin. Surveillance endoscopy findings from patients after overnight fasting have shown food retention in 14–38 % of patients after subtotal gastrectomy, but this finding is often not associated with symptoms of delayed gastric emptying [8].

Anastomotic Leaks Anastomotic leakage occurs in 5–10 % of patients undergoing total gastrectomy for gastric cancer [2, 9, 10]. The majority of leaks can be treated conservatively without reoperation. Anastomotic leakage significantly increases mortality and also appears to be associated with poor oncologic prognosis [10, 11]. In a large series of over 1000 total gastrectomies performed over a 30-year period, the associated mortality rates were 19 % in patients with anastomotic leakage treated without surgery and 64 % in patients treated with surgery [9]. The increased mortality rates associated with reoperative surgery have led to efforts to manage leaks nonoperatively. Endoscopic stent placement has been shown to be a safe procedure to manage anastomotic leaks conservatively after gastrectomy and esophagectomy. Although most series are small, successful healing rates for patients with an anastomotic leak treated with stent placement range from 75 to 90 % [12, 13].

Duodenal Stump Leak The duodenal stump is a relatively infrequent site of leakage after subtotal or total gastrectomy, with reported frequency rates of 2–3 % [3, 14, 15]. Leakage from the duodenal stump with resultant inflammation has also been reported as a negative prognostic factor for overall survival after surgery for gastric cancer [14]. Management may be nonoperative with percutaneous drain placement or may require reoperation with drain placement, although further attempts at duodenal stump closure are rarely successful. Figure 17.1 shows a computed tomography (CT) image of a patient with a duodenal stump leak after subtotal gastrectomy.

Late Postoperative Complications

Dumping Syndrome

Dumping syndrome can be classified on the basis of time (*early* versus *late*) and symptom type (*vasomotor* versus *gastrointestinal*). *Early dumping* typically occurs within 30 min of eating, whereas late dumping occurs several hours after eating. Early dumping syndrome is likely the result of the rapid emptying of hyperosmolar food into the small bowel. Owing to the rapid hyperosmolar load into the bowel, fluid shifts into the bowel and causes a sympathetic response [16]. Excessive

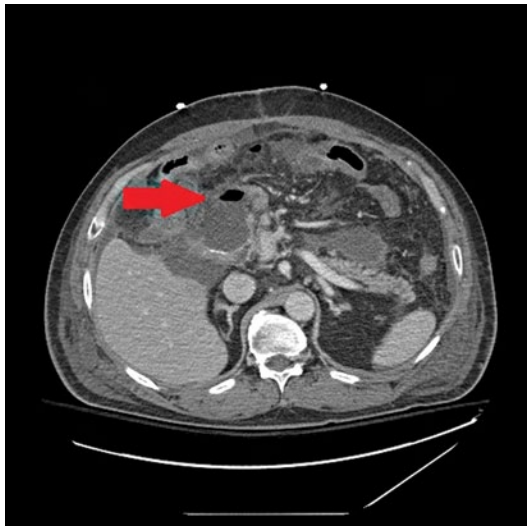

Fig. 17.1 Computed tomography (CT) image of a patient with duodenal stump leakage after subtotal gastrectomy. *Red arrow* indicates fluid and air at duodenal stump staple line

gastrointestinal hormone secretion into the bowel and local peristaltic responses also play a role in this syndrome. Early dumping syndrome symptoms often include nausea, abdominal cramping, diarrhea, tachycardia, and possibly hypotension. *Late dumping* is often attributed to the aggressive insulin response to hyperglycemia induced by the rapid emptying of carbohydrate-rich food into the small bowel and occurs within 2–3 h after a meal. The insulin response leads to subsequent hypoglycemia, with symptoms such as fatigue, weakness, and diaphoresis. *Vasomotor predominant* dumping includes flushing, diaphoresis, palpitations, and tachycardia. *Gastrointestinal predominant* dumping includes symptoms of nausea, emesis, abdominal pain and cramping, and diarrhea.

Diagnosis

As dumping is a relatively frequent postgastrectomy issue, diagnosis is made predominantly based on the presence of typical symptoms and inciting factors. In a large survey of over 1000 gastrectomy patients, 68% of patients had early dumping syndrome, and 38% had late dumping syndrome [17]. Although criteria for dumping syndrome have been developed on the basis of a 50-g glucose provocative test, subjective symptoms remain the mainstay of diagnosis [18]. Diagnosis can also be confirmed with improvement from dietary modifications. Patients with early dumping syndrome are susceptible to developing late dumping syndrome. Patients who lose more weight after surgery are also prone to dumping syndrome [17].

Medical Management

Dietary management is the primary treatment modality for dumping syndrome and is often successful. Patients should avoid foods with high levels of simple carbohydrates (sugar) and attempt to eat small, frequent meals with foods high in fiber and protein. Patients should eat 6–8 meals per day and restrict fluids while eating. Vasomotor-predominant dumping symptoms can be improved if the patient rests in the supine position for 20–30 min after eating. Severe dumping syndrome refractory to standard dietary changes may be improved with octreotide [19, 20]. Long-acting repeatable (LAR) intramuscular octreotide injection appears to be as effective at improving postoperative dumping as short-acting subcutaneous octreotide. The LAR form of octreotide has the obvious benefit of monthly injection compared with three injections per day of the short-acting formulation. Comparison studies have shown that the LAR form of octreotide improves quality of life scores [20]. Limitations to octreotide therapy include an apparent tolerance to the therapeutic effect and long-term side effects that include gallstones, diarrhea, and steatorrhea [21, 22].

Surgical Treatment

With the decrease in surgery for peptic ulcer disease, the high rates of success in treating dumping syndrome with medical management, and the natural history of gastric cancer, surgery is an extremely rare treatment for dumping syndrome and is primarily of historical interest. In addition, there is no clear consensus on the optimal surgical intervention for dumping syndrome. The

most commonly suggested surgical treatment is to create a Roux-en-Y gastrojejunostomy. In patients with a previous Billroth II loop gastrojejunostomy, the afferent jejunal limb is transected and anastomosed 60 cm distal to the gastrojejunostomy. In patients with a previous Billroth I gastroduodenostomy, the duodenum is transected, additional gastrectomy is performed, and a Roux-en-Y reconstruction is performed. Another reported option is the reversed jejunal interposition graft, described as the interposition of an antiperistaltic jejunal segment between the stomach and duodenum. However, most reports of this operation are old enough to question whether it should still be considered an option [23].

Afferent Limb Syndrome

Afferent limb syndrome is a partial or complete obstruction of the small bowel involving the afferent limb and anastomotic site after loop gastrojejunostomy. Creation of a loop gastrojejunostomy involves an afferent limb of proximal jejunum that transports bile and pancreatic fluid to the stomach. The efferent limb is the distal limb of the anastomosis and transports bile, pancreatic fluid, and gastric contents distally into the jejunum. Obstruction of the afferent limb can be secondary to adhesions, internal hernia formation, stenosis owing to cancer recurrence or ulceration, and intussusception. There is some controversy as to predisposing factors, but most authors report that afferent limb obstructions are more common in patients with longer afferent limbs and with an anastomosis of the afferent limb to the lesser curvature of the stomach [24]. Retrocolic placement is occasionally mentioned as a preventative procedure for afferent limb syndrome secondary to adhesions, but this procedure does increase the risk of an internal hernia through the mesocolic defect.

Diagnosis

Classical symptoms of afferent limb syndrome include intermittent epigastric/right upper quadrant pain relieved by bilious emesis. The abdominal pain is often described as cramping or colicky, and the bilious emesis can be forceful or even projectile. Afferent limb syndrome in the immediate postoperative period must be differentiated from postoperative gastroparesis or ileus and must be treated promptly to prevent a duodenal stump leak. The more chronic form of afferent limb syndrome can have a presentation similar to bile reflux gastritis. Most afferent limb syndromes are diagnosed with CT imaging, which not only documents the site of obstruction but also reveals potential malignant obstructions or metastatic disease in patients with a history of cancer. Figure 17.2a, b demonstrate CT images of a patient with afferent limb syndrome secondary to recurrence of gastric cancer at the gastroje-

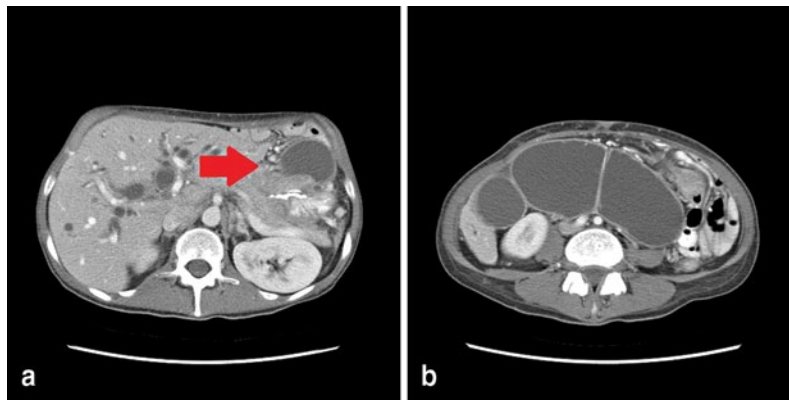

Fig. 17.2 **a** Computed tomography (CT) image of a patient with afferent limb syndrome due to recurrence of gastric cancer at gastrojejunostomy staple line (*red arrow*). **b** CT image of dilated duodenum in a patient with afferent limb syndrome

junostomy performed with subtotal gastrectomy. Historical reports often mention that hepatobiliary iminodiacetic acid (HIDA) scans of patients with afferent limb syndrome follow the flow of radiolabeled bile into the obstructed afferent limb with minimal or no transit into the remaining gastrointestinal tract. Endoscopy can be helpful to determine the etiology of obstruction such as gastric remnant-related malignancy, cancer recurrence, and marginal ulceration or stenosis.

Medical Management

In the immediate postoperative setting, afferent limb obstruction can require emergency surgery and should be suspected in situations of duodenal stump leakage. In nonemergent situations, medical management can include a trial of nasogastric tube decompression and hydration, although a nasogastric tube may not decompress the afferent limb adequately. Stent placement or endoscopy with dilation also is an option for nonsurgical management.

Surgical Management

There are two main options for surgical correction of afferent limb syndrome; revision of the existing gastrojejunostomy is usually not one of these options. First, and simplest, is a jejunojejunostomy between the afferent and efferent limbs, sometimes referred to as a Braun enteroenterostomy. This approach requires minimal dissection and no bowel transection and should be an option in most patients. Although creating a shorter afferent limb during the initial surgery can prevent afferent limb syndrome, a shorter limb can also prevent enteroenterostomy as an option for treating this postoperative complication. The second option for treating afferent limb syndrome is converting the original surgery into a traditional Roux-en-Y gastrojejunostomy. This approach also involves leaving the existing gastrojejunostomy in place, transecting the afferent limb close to the stomach, and creating a 60-cm Roux limb with a jejunojejunostomy between the transected afferent limb and the efferent limb 60-cm distal to the gastrojejunostomy. If the patient has any history of bile reflux gastritis, the Roux-en-Y gastrojejunostomy should be considered.

Efferent Limb Syndrome

Efferent limb syndrome refers to a mechanical obstruction at or distal to the Billroth II gastrojejunostomy. Symptoms include traditional symptoms of obstruction such as nausea, emesis, and distention but can include bilious emesis similar to delayed gastric emptying, bile reflux gastritis, and afferent limb syndrome. Adhesions or stenosis secondary to marginal ulceration are benign causes of obstruction, whereas local recurrence or carcinomatosis can represent malignant causes.

Diagnosis

To differentiate efferent limb syndrome from other causes of bilious emesis, physicians should use CT scans or esophagogastroduodenoscopy. A HIDA scan can be helpful in more chronic situations to differentiate efferent limb syndrome from bile reflux gastritis. A gastric emptying scan or upper gastrointestinal fluoroscopy may be required to differentiate efferent limb syndrome from delayed gastric emptying.

Medical Management

Surgery is the preferred treatment of efferent limb syndrome with benign causes of stenosis or obstruction. For malignant etiologies, treatment should balance estimated prognosis, perioperative risk, extent of surgery, and oncologic treatment options. Options include stent placement, venting gastrostomy tubes, and antisecretory medications such as octreotide.

Surgical Management

As in afferent limb syndrome, revision of an anastomotic stricture is rarely an option in efferent limb syndrome. In a patient with favorable anatomy after the initial gastrojejunostomy and with operative risk favoring less extensive surgery, a gastrointestinal anastomosis stapler can be used to extend the anastomotic stricture either proximally or distally. The gastrostomy and enterotomy from this revised anastomosis can then be closed with interrupted sutures or with a thoracoabdominal stapler. Most patients, especially those with a high suspicion for bile reflux gastritis, are treated with resection of the anastomosis and a Roux-en-Y reconstruction. Patients with delayed gastric emptying can be considered for resection of the anastomosis with new Billroth II reconstruction and enteroenterostomy downstream to prevent bile reflux gastritis.

Roux Stasis Syndrome

Roux stasis syndrome is a disorder of gastric remnant or upper intestinal motility that manifests with symptoms (most often postprandial) of nausea, emesis, and abdominal pain. The syndrome is attributed to the effects of vagotomy and proximal small bowel transection. Small bowel transection disrupts the cyclical electrical charges and action potentials that spread distally along the small bowel and coordinate peristaltic muscle contractions. Patients who underwent a Roux-en-Y gastrojejunostomy had consistently slower transit than did control subjects; however, these findings do not correlate to symptoms [25]. Symptoms of upper gastrointestinal dysmotility after gastric resection and Roux-en-Y gastrojejunostomy are multifactorial, and few recent studies have investigated diagnosis and treatment of this complication. The study of this syndrome was more relevant in the past when surgery was mainly performed to treat peptic ulcer disease. Roux stasis syndrome is infrequently encountered after gastric cancer surgery and almost never requires operative intervention.

Diagnosis

There are early (within 90 days of surgery) and late variants of Roux stasis syndrome. Suspicion of Roux stasis syndrome should be maintained in patients with postprandial symptoms of pain, nausea, and emesis. As in other postgastrectomy syndromes, the diagnosis of Roux stasis syndrome is one of exclusion after ruling out mechanical forms of obstruction, infections, and technical complications.

1. Early—Must be differentiated from postoperative gastroparesis or early postoperative small bowel obstruction. CT imaging is the primary modality to rule out postoperative mechanical obstruction, but upper gastrointestinal fluoroscopy or endoscopy can also be useful. The diagnosis is often made in the setting of a normal CT scan in patients with symptoms of gastroparesis that persist longer than the typical clinical scenario of postoperative gastroparesis or ileus.
2. Late—Differential diagnosis of late Roux stasis syndrome includes anastomotic stricture, adhesive bowel obstruction, internal hernia, and malignant bowel obstruction. CT imaging, fluoroscopy, endoscopy, and nuclear medicine gastric emptying studies may be helpful in diagnosing late Roux stasis syndrome.

Medical Management

There are few good surgical options for this syndrome, and therefore medical management is the main treatment modality. A thorough history can help to elicit factors or meals that exacerbate postprandial symptoms. Dietary modification with small, frequent meals is often helpful. Liquids will typically empty better than solids and may improve symptoms. Nutritional liquid supplements between meals are often crucial in providing enough calories with small meals. Metoclopramide and erythromycin, although not good long-term medications, can be helpful in the short term in breaking the cycle of the patient's symptoms.

Surgical Management

Surgical intervention in patients with Roux stasis syndrome often focuses on two main procedures: (1) resection of the remnant stomach with near-total or total gastrectomy, and (2) feeding tube placement.

Bile Reflux Gastritis

Patients who undergo pyloroplasty, gastroduodenostomy (Billroth I), and loop gastrojejunostomy (Billroth II) are predisposed to bile reflux gastritis. Bile reflux gastritis, similar to other postgastrectomy syndromes, is becoming as infrequent as surgery for peptic ulcer disease owing to the accumulating evidence for the superiority of Roux-en-Y reconstruction over other means of reconstruction after gastrectomy for gastric cancer. In a study using an intragastric bile monitor and endoscopic evaluation, surgeons from Japan have demonstrated less bile reflux and remnant gastritis in patients who underwent Roux-en-Y reconstruction than in those who underwent Billroth I and II reconstruction [26]. The long-term results of a prospective randomized trial of Billroth II and Roux-en-Y reconstruction after gastrectomy for peptic ulcer disease showed improved patient-reported outcomes, improved endoscopic findings, and less histologic evidence of gastritis in patients who underwent Roux-en-Y gastrojejunostomy [27].

Bile reflux gastritis is most commonly diagnosed by the findings of abdominal pain, nausea, bilious emesis, and bile and inflammation in the stomach. Most, if not all, patients who have undergone a distal gastrectomy with Billroth I or II reconstruction will have bile and inflammation in the stomach, which makes diagnosing bile reflux gastritis challenging. The indications for surgical intervention in this disease should take into account other etiologies as a cause of the patient's symptoms. Other etiologies to consider in the differential diagnosis are nonbilious reflux, gastroparesis, marginal ulceration, peptic ulcer disease, afferent/efferent limb syndromes, adhesive bowel obstruction, malignant bowel obstruction, and chronic abdominal pain owing to previous surgery.

Diagnosis

Considering the broad differential diagnosis, the likely multifactorial etiology of the patient's symptoms, and the modest outcomes associated with surgical intervention, physicians should perform an extensive diagnostic workup of patients with possible bile reflux gastritis and should approach this diagnosis with a "diagnosis of exclusion" mentality. Endoscopy is essential to document bile reflux and gastritis. A CT scan of the chest, abdomen, and pelvis should be considered in patients with a history of malignancy to rule out metastatic disease and recurrence as a cause of symptoms before performing an extensive operation. A HIDA scan can also be helpful to document pooling of bile within the stomach. An upper gastrointestinal series is appropriate to evaluate not only postoperative anatomy and function but also obstruction. Similarly, a gastric emptying scan is crucial to rule out gastroparesis, which can be worsened by further operation.

Medical Management

Cholestyramine, a bile acid-binding resin, is generally ineffective for treating bile reflux gastritis owing to this medication's rapid transport through the stomach. In one study, patients treated with cholestyramine plus alginates to help reduce transit out of the stomach had no difference in symptoms, endoscopic findings, or histologic findings than did the placebo group [28]. Sucralfate, a medication that coats the surface of the stomach to protect against acid and bile salts, may last for up to 6 h with minimal side effects. In a small placebo-controlled trial of 23 patients, after 6 weeks of treatment, the sucralfate-treated group demonstrated improvement in histologic inflammation but no improvement in symptoms [29]. Ursodeoxycholic acid's mechanism of action is to reduce the cholesterol content of bile and the reabsorption of cholesterol by the intes-

tines. One small study of 12 patients reported that patients treated with ursodiol had fewer symptoms associated with bile reflux gastritis than did the placebo group [30].

Surgical Management

Definitive treatment of bile reflux gastritis usually requires surgery, although success varied from 47 to 91% in studies from an era when surgery was more frequently performed to treat peptic ulcer disease [31–34]. Although most patients with gastric cancer who experience bile reflux gastritis will have had a Billroth II gastrojejunostomy, surgical treatment is similar after Billroth I gastroduodenostomy, and Roux-en-Y gastrojejunostomy is the most common recommendation.

For patients with Billroth I anatomy, the duodenum is transected distal to the anastomosis, and the stomach is transected. The remnant stomach volume depends on the presence of gastroparesis; patients with gastroparesis will benefit from subtotal gastrectomy with less stomach remnant. For patients with Billroth II anatomy, the two main options include Braun enteroenterostomy and Roux-en-Y gastrojejunostomy. For Braun enteroenterostomy, the anastomosis is performed between the afferent and efferent limbs of the Billroth II gastrojejunostomy. The efferent limb of the anastomosis is typically anastomosed between 45 and 60 cm distal to the gastrojejunostomy to prevent continued bile reflux gastritis. For conversion to a Roux-en-Y gastrojejunostomy in a patient who requires additional gastrectomy, the afferent and efferent limbs are transected close to the stomach, and a 60-cm Roux limb is created. In patients not requiring additional gastrectomy, the afferent limb is divided close to the stomach and anastomosed to the efferent limb to create a 60-cm Roux limb.

Postvagotomy Diarrhea

Postvagotomy diarrhea is a syndrome of unclear etiology that occurs in a minority of patients after truncal vagotomy. Although gastric resection is not required for postvagotomy diarrhea, many patients have concomitant gastric procedures, and this disorder is often classified with other postgastrectomy syndromes. Although the pathophysiology of this disorder has not been clearly identified, the syndrome is likely the result of alteration in pacemaker function, intestinal motility, hypoacidity, malabsorption, bacterial overgrowth, or a combination of these factors.

Diagnosis

Another possible diagnosis often considered in patients with diarrhea after gastrectomy and vagotomy is dumping syndrome. When compared with dumping syndrome, postvagotomy diarrhea often involves more frequent bowel movements, no relation to oral intake, and often occurs consistently throughout the day and night. Rarely, postvagotomy diarrhea can result in fatigue, hypovolemia, and malnutrition.

Medical Management

Dietary modification is an essential component of medical management and attempts should be made to identify causative foods. Commonly reported inciting foods are caffeine and milk products. Dietary fiber supplements may help to improve diarrhea. Medical management includes loperamide, diphenoxylate, and possibly antibiotics to rule out bacterial overgrowth. A trial of octreotide may also be warranted. Patience during treatment is required for the patient and physician, as there are few surgical options and symptoms may take several months to resolve.

Surgical Management

Surgical intervention is primarily of historical interest and is seldom required for postvagotomy diarrhea. The most reported procedure is a 10-cm reversed jejunal segment in the distal jejunum. This antiperistaltic procedure mechanically slows transit time and may facilitate better absorption.

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Hereditary Diffuse Gastric Cancer

18

George Poultsides and Jeffrey A. Norton

Gastric cancer is the fourth most common cancer worldwide, and is the second leading cause of cancer death [1]. Environmental agents, including *Helicobacter pylori* infection and diet are the primary risk factors for stomach cancer, but approximately 10 % of gastric cancers are a result of hereditary factors [2, 3]. Histologically, gastric cancers may be classified as either diffuse type or intestinal type. The intestinal type is linked to environmental factors and advanced age. The diffuse type happens in younger patients and occurs in families. Because of a significant decrease in the more common intestinal type of gastric cancer, the overall incidence of gastric cancer has decreased. However, the incidence of diffuse gastric cancer that is also called signet ring cell or linitis plastica, has either increased or remained stable.

Hereditary diffuse gastric cancer (HDGC) is a genetic cancer susceptibility syndrome diagnosed by one of the following: (1) two or more documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least one diagnosed before the age of 50, (2) three or more cases of diffuse gastric cancer in first- or second-degree relatives, independent of age of onset. The average age of onset of HDGC is 38. It is inherited as an autosomal dominant [4].

In 1998 inactivating germline mutations in the E-cadherin gene *CDH1* were identified in three Maori families with diffuse gastric cancer [5]. The CDH1 mutations in these families had an autosomal dominant pattern with high, but not complete, penetrance. Clinically apparent stomach cancer occurred at a young age with the youngest affected individual dying at the age of 14 [5]. Germline mutations of CDH1 have been detected in 30–50 % of all patients with HDGC [3, 6]. More than 50 mutations have been seen across diverse ethnic backgrounds including all nationalities [3]. In addition to gastric cancer, patients with germ line CDH1 mutations have an increased risk of lobular breast cancer and this may present prior to stomach cancer in some individuals [7]. CDH1 is the only gene that has been found to be present in HDGC. Approximately 70–80 % of individuals with a germ line CDH1 mutation develop diffuse gastric cancer [8], but it may be even higher. The need for a systematic dissection of stomach gastrectomy specimens is supported by a recent study that shows that negative gastrectomy specimens had invasive carcinoma on more detailed analysis.

CDH1 is located on chromosome 16q22.1 and encodes the calcium-dependent cell adhesion glycoprotein E-cadherin. Functionally, E-cadherin impacts maintenance of normal tissue morphology and cellular differentiation. CDH1 acts as a tumor suppressor gene in HDGC, with

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loss of function leading to loss of cell adhesion and subsequently to proliferation, invasion, and metastases. The germ line CDH1 mutation is a truncating mutation. Missense mutations have been reported but their functional significance is unknown. In vitro assays for cellular invasion and aggregation may predict the functional impact of missense mutations [6]. Within the gastric mucosa, the "second hit" leading to complete loss of E-cadherin function (Fig. 18.1) results from CDH1 promoter methylation as in sporadic gastric cancer [9].

Recommended screening criteria for CDH1 mutations are as follows:

- Families with one or more cases of diffuse gastric cancer.
- Individuals with diffuse gastric cancer before the age of 40 years without a family history.
- Families or individuals with cases of diffuse gastric cancer (one case below the age of 50 years) and lobular breast cancer.
- Cases where pathologists detect in situ signet ring cells or pagetoid spread of signet ring cells adjacent to diffuse type gastric cancer [2, 10].

After obtaining informed consent, a team comprising a geneticist, gastroenterologist, surgeon, and oncologist should discuss the possible outcomes of testing and the management options. Genetic testing should first be performed on a family member with HDGC or on a tissue sample if no affected relative is living. In addition to direct sequencing, multiplex ligation-dependent probe amplification is recommended to test for large genomic rearrangements. If a CDH1 mutation is identified, asymptomatic family members may proceed with genetic testing, preferably by the age of 20 [4]. If no mutation is identified in a family member with diffuse gastric cancer, the value of testing others is negligible so testing is not indicated.

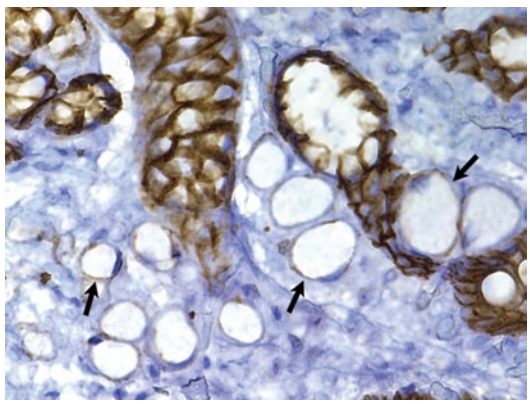

Fig. 18.1 Hereditary diffuse gastric cancer (HDGC) is associated with loss of E-cadherin gene expression. Immunohistochemistry of E-cadherin expression (*brown* cells) in a patient with HDGC demonstrates that the signet ring cancer cells (*arrows*) no longer express E-cadherin (lack of brown color). (From Norton et al. [3]. Reprinted with permission from Wolters Kluwer Health)

Among individuals found to carry a germ line CDH1 mutation, clinical screening for stomach cancer has been poor. Histologically, diffuse gastric cancer is characterized by multiple infiltrates of malignant signet ring cells that may underlie normal mucosa [11]. Because these malignant foci are small in size and widely distributed, they are difficult to identify via random endoscopic biopsy. Chromoendoscopy and positron emission tomography (PET) have reportedly been used, but the clinical utility of these tools in early detection is minimal. Lack of a sensitive screening test for HDGC makes early diagnosis problematic. By the time patients are symptomatic and present for treatment, patients have diffuse stomach cancer or linitis plastica, and prognosis is poor (Table 18.1). Published case reports describe patients who have extensive diffuse gastric cancer despite normal endoscopy with biopsies [12]. The 5-year survival rate for individuals who develop clinically apparent diffuse gastric cancer is only 10 %, with the majority dying before age 40.

Because of high cancer penetrance, poor outcome, and inadequacy of clinical screening tools for HDGC prophylactic total gastrectomy is recommended for asymptomatic CDH1 mutation carriers [2]. Although total gastrectomy is prophylactic, most specimens have multiple foci of diffuse signet ring cell cancer [3, 12, 13]. This is seen even in patients who have undergone extensive screening, including high-resolution computed tomography (CT), PET scan, chromoendoscopy-guided biopsies, and endoscopic ultrasonography [3]. However, HGDC

Table 18.1 Outcome of patient with hereditary diffuse gastric cancer based on symptoms. Patients who were diagnosed not by symptoms but presence of CDH1 mutation did better. Each had cancer and was cured by total gastrectomy, while only 20% of patients who presented with symptoms were cured. No patient died from gastric cancer in the asymptomatic group, while 60% died in the symptomatic group. (Data are from Chen et al. [17])

n	Symptoms	Age (range) y	Positive endoscopy (%)	Disease-free (%)	Dead of disease (%)
13	No	48 (18–70)	2 (15)	100	0 (0)
5	Yes	40 (23–52)	5 (100)	20	3 (60)

in asymptomatic CDH1 carriers is usually completely resected by prophylactic gastrectomy, as pathological analysis of resected specimens shows only T1N0 disease.

Because these signet ring cell cancers are multifocal and distributed throughout the entire stomach, especially in the cardia [14] prophylactic gastrectomy must include the entire stomach (Table 18.2). Furthermore, it should be performed by a surgeon experienced in the technical aspects of the procedure and familiar with HDGC. In asymptomatic patients, lymph node metastases are usually not detected; although, D2 lymph node resection is still recommended. The optimal timing of prophylactic gastrectomy in individuals with CDH1 mutations is unknown, but most recommend that it be performed 5 years earlier than the youngest patient in the family with HDGC [2].

Although it is potentially lifesaving, prophylactic gastrectomy for CDH1 mutation carries significant risks. Overall mortality for total gastrectomy is estimated to be between 2 and 4%. Further, there is some long-term morbidity including diarrhea, dumping, weight loss, and difficulty eating [3]. A recent study of the effects of prophylactic gastrectomy for CDH1 mutation demonstrated that 70% had diarrhea, 63% fatigue, 81% eating discomfort, 63% reflux, 45% eating restrictions, and 44% had altered body image [15]. Because of these complications and the fact that lymph node spread has not been observed, some recommend vagus-preserving gastrectomy done either open or laparoscopically. In addition, because the penetrance of CDH1 mutations is incomplete, prophylactic gastrectomy has been performed in several patients without gastric cancer [14].

Some individuals with CDH1 mutations choose not to pursue prophylactic gastrectomy. These individuals should undergo careful surveillance, including biannual chromoendoscopy with biopsies, beginning when they are at least 5 years younger than the youngest family member with diffuse gastric cancer at time of diagnosis. It is recommended that any endoscopically visible lesion is targeted and that six random biopsies are taken from the following regions: antrum, transitional zone, body, fundus, and cardia. Most cancers have been detected in the more proximal stomach near the cardia. Careful white-light examination with targeted and random biopsies combined with detailed histopathology can identify early lesions and help to inform decision making with regard to gastrectomy [16]. Additionally, because women with CDH1 mutations have a nearly 40% lifetime risk of developing lobular breast carcinoma, they should be carefully screened with annual mammography and breast MRI starting at age 35 [7]. They should also do monthly self-examinations and every 6 months have a breast examination by a physician.

Table 18.2 Distribution of signet ring cell hereditary diffuse gastric cancer in 8 asymptomatic patients who were diagnosed by CDH-1 mutation. Signet ring cell cancer was present in multiple sites in each patient and although it was distributed throughout the entire stomach the most common site was the cardia. This demonstrates the need for total gastrectomy. (Data are from Rogers et al. [14])

	A	B	C	D	E	F	G	H
Cardia	10	12	16	14	5	10	2	1
Body	3	2	6	3	0	1	0	0
Antrum	2	1	1	2	1	3	1	1

The emergence of gene-directed gastrectomy as a treatment strategy for patients with HDGC represents the culmination of a successful collaboration between molecular biologists, geneticists, oncologists, gastroenterologists, and surgeons. It is anticipated that the recognition of similar molecular markers in other familial cancer syndromes will transform the approach to the early diagnosis and treatment of a variety of tumors.

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Surveillance After Gastric Resection

19

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Introduction

Cancer surveillance after treatment is a complex issue in oncology as cancer treatments continue to evolve and patients are surviving longer. The choice of a follow-up program is a challenging topic and it should theoretically take into account survival and quality-of-life issues as well as the burden of surveillance tests, and their financial costs.

The potential value of a surveillance program in patients who have undergone cancer surgery is to detect recurrences in the early and asymptomatic period, to identify complications associated with surgery and to collect outcome data. Early detection of cancer recurrence may be associated with improved survival because it may provide an opportunity for treatment to be initiated while the patient's condition is sufficiently stable to receive effective therapy.

Postoperative follow-up schedule is recommended for nearly all cancers in international guidelines, even if the value of postoperative surveillance remains controversial [1, 2].

In colorectal and breast cancers several randomized controlled trials and meta-analyses have demonstrated an overall survival advantage associated with detection [3, 4].

Gastric cancer is one of the most frequent malignancies and the second leading cause of cancer deaths worldwide with 989,600 new cases and 738,000 deaths in 2008, accounting for 8 % of the total cases and 10 % of total deaths due to cancer [5].

Recurrence is the most important factor associated with death even after potentially curative gastrectomy. Over two-thirds of recurrences occur in the first 3 years following surgery and fewer than 10 % occur after 5 years; given the poor survival of patients with recurrent gastric cancer only palliative therapy is generally possible [6, 8].

Most clinicians perform postoperative surveillance for their gastric cancer patients during the first 3 years after surgery. However, there is no consensus on the most appropriate regimen and frequency of follow-up after curative surgery [9].

It must also be said that patients could be possibly reassured from regular follow-up, although

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psychological benefit of surveillance is debatable.

There is a wide variation in recommendations for surveillance among experts. In recent years an increasing focus on evidence-based medicine that has coincided with growing concern about costs and efficiency in medicine has caused a re-evaluation of surveillance practices.

To date, all of the recommendations on surveillance are based on low-level evidence or no evidence at all given the complete lack of randomized controlled trials on this peculiar subject. Very few report anything other than the detection of recurrences or death as the primary endpoints, and given the poor survival of patients with an ascertained recurrent gastric cancer, the prognostic effect of early detection seems doubtful [9].

The objective of this chapter is to review the literature about the efficacy of follow-up protocols and investigations after gastrectomy for cancer.

Evidences from Medical Literature

Every medical literature review to date has failed to show high-level evidence about any follow-up schedule to be applied for curatively resected gastric cancer patients. All data are retrospective and observational, thus preventing any definitive conclusion.

We have selected seven studies and one systematic review concerning follow-up after surgery for gastric cancer (Table 19.1).

All these studies focused on the possible survival benefit of early detection of recurrence by intensive postoperative surveillance.

Four studies indicated that an intense postoperative follow-up protocol was successful in identifying asymptomatic recurrences earlier than symptomatic recurrences with an improvement in post-recurrence survival [11]. Nevertheless, they could not achieve any evident advantage in overall survival [8, 10, 12]. Overall survival was reported only by two of these studies but estimated survival did not show any statistically significant difference between patients who underwent an intensive follow-up schedule.

With this purpose a study from Memorial Sloan-Kettering Cancer Center [13] showed that follow-up did not detect asymptomatic recurrences earlier than symptomatic recurrences in patients with gastric cancer who underwent a curative gastrectomy. In this report patients with asymptomatic recurrences showed better post-recurrence and disease-specific survival than those with symptomatic recurrences; in their conclusions the authors suggest that symptomatic and asymptomatic recurrence patterns are possibly different in their biological behavior and are associated with different survival outcomes. Similarly, in a paper by Kim et al. [14] median overall survival and post-recurrence survival were worse for patients with a symptomatic recurrence than for those with an asymptomatic recurrence. Moreover, in this study, multivariate analysis revealed that the presence of a symptomatic recurrence and the disease-free interval were independent prognostic indicators for post-recurrence survival. Furthermore, asymptomatic patients had a major benefit from re-resection and post-recurrence chemotherapy and at multivariate survival analysis the presence of symptoms was the only independent factor of poor survival suggesting a more biologically aggressive disease in symptomatic patients. Bilici et al. [15], in a study on 173 patients with recurrent gastric

Table 19.1 Evidences from medical literature

Paper	Conclusions
Mikani et al. [12]	An intensive follow-up is successful in identifying asymptomatic recurrences earlier. Improvement in post-recurrence survival for the asymptomatic groups
Bohner et al. [10]	
Tan et al. [11]	An intensive follow-up is successful in identifying asymptomatic recurrences earlier. Improvement in post-recurrence survival for the asymptomatic groups. *No advantage in overall survival*
Kodera et al. [8]	
Bennett et al. [13]	Intensive follow-up does not detect asymptomatic recurrences earlier. Asymptomatic and symptomatic recurrence patterns are biologically different and associated with different survival outcomes
Kim et al. [14]	
Bilici et al. [9]	

cancer, found that symptomatic recurrence is an important prognostic factor for post-recurrence survival and that presence of symptoms may be considered a marker of biologic tumor aggressiveness, which is an important determinant of survival at the time of recurrence diagnosis during follow-up for gastric cancer.

A recent systematic review by Cardoso et al. reviewed five studies enrolling a total of 810 patients and assessing outcomes of follow-up after gastrectomy for gastric cancer [16].

This review did not find any evidence suggesting that postoperative surveillance has any survival benefit; it has been also stressed that no such study has ever addressed quality-of-life issues. Major limitations in current literature were the study design and a lead-time bias in which the observed prolonged survival is due to earlier detection of recurrence, rather than to an effect on disease outcome.

International Guidelines and High-Volume Center Recommendations

The lack of evidence of follow-up is revealed by the fact that the most leading scientific societies and cooperative groups propose different schedules and that many centers apply a follow-up program dictated by past common practices in their medical center. Guidelines are generally supposed to be founded on strong evidence (therefore valid and unbiased) but to date they are based on low-level evidence or no evidence at all (Table 19.2).

The *American Society of Clinical Oncology* (www.asco.org), the *Society of Surgical Oncology* (www.surgoncol.org), the *Cancer Care Ontario* (www.cancercare.on.ca), the *National Institute for Clinical Excellence* (www.nice.org.uk), the *Cochrane Collaboration* (www.cochrane.org), and the *Society for the Surgery of the Alimentary Tract* (www.ssat.com) do not provide formal guidelines or recommendations for follow-up after gastrectomy for cancer. Similarly, the *Japanese Gastric Cancer Association* (JGCA) guidelines offer no guidelines on follow-up [17].

The *National Cancer Comprehensive Network* (NCCN) guidelines include for all patients a complete history and physical examination every 3–6 months for 1–2 years, every 6–12 months for 3–5 years and annually thereafter. Other investigation should be done if clinically indicated. Patients who have undergone surgical resection should be monitored and treated as indicated for vitamin B_{12} and iron deficiency [2].

The *European Society of Medical Oncology* (ESMO), the *European Society of Surgical Oncology* (ESSO), and the *European Society of Radiotherapy and Oncology* (ESTRO) guidelines state that regular follow-up may allow treatment of symptoms, psychological support, and early detection of recurrence, though there is no evidence that it improves survival outcomes. Follow-up has a role in the identification of patients for second-line chemotherapy and in clinical trials to detect symptoms of disease progression before significant clinical deterioration. Laboratory and imaging studies should be carried out when recurrence is suspected or when further chemo- or radiotherapy is indicated [1].

The *Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland* (AUGIS), *the British Society of Gastroenterology* (BSG), and the *British Association of Surgical Oncology* (*BASO*) agree that regular review may identify early recurrence but there is no evidence for specific investigations nor that follow-up can affect overall survival. Endoscopy, cross-sectional imaging, and tumor markers have all been evaluated, but lack specificity or sensitivity [18].

The Italian Research Group for Gastric Cancer (*GIRCG*) has proposed three different follow-up schedules (mild, moderate, or intensive) after gastrectomy for cancer in relation with a risk score calculated for each individual patient. A logistic regression model is used for the computation of the score; the coefficient Z is calculated as $Z = -3.888$–0.339 (middle third) $+0.917$ (upper third) $+6.266$ (diffuse location) $+0.027$ (age) $+1.075$ (pT2) $+2.013$ (pT3-T4) $+1.668$ (pN1) $+3.056$ (pN2) $+4.971$ (pN3) -0.848 (D2–D3 dissection). The value of parametric variables

Table 19.2 International guidelines recommendations

Society	Guidelines for follow-up
ASCO (American Society of Clinical Oncology)	No guidelines
JGCA (Japanese Gastric Cancer Association)	No guidelines
SSO (The Society of Surgical Oncology)	No guidelines
CCO (Cancer Care Ontario)	No guidelines
NICE (National Institute for Clinical Excellence)	No guidelines
CC (Cochrane Collaboration)	No guidelines
SSAT (Society for the Surgery of the Alimentary Tract)	No guidelines
AUGIS (Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland), *BSG* (British Society of Gastroenterology), *BASO* (British Association of Surgical Oncology)	No guidelines
NCCN (National Comprehensive Cancer Network)	Visit every 3–6 months for 1–2 years, every 6–12 months for 3–5 years and annually thereafter. Exams only if clinically indicated
ESMO (European Society for Medical Oncology), *ESSO* (European Society of Surgical Oncology), *ESTRO* (European Society of Radiotherapy and Oncology)	No guidelines. Follow-up should be performed in the identification of patients for second-line chemotherapy and in clinical trials.
GIRCG (Italian Research Group for Gastric Cancer)	Mild (risk < 10%): tumor markers and US every 6 months, EGDS and X-ray annually, CT scan if clinically indicated or increased level of markers. Moderate (risk 10–50%): tumor markers every 3 months, US every 6 months, EGDS and CT scan annually. Intensive (risk > 50%): tumor markers every 3 months, CT scan every 6 months, EGDS annually. After the first 5 years visit annually and exams if clinically indicated

was 0 (negative) or 1 (positive), whereas age was considered as a continuous variable. For each patient, the value of the coefficient Z obtained was included in the formula: $(e^Z/1+e^Z)\times 100$ which gives risk values ranging from 0 to 100 % [19].

For patients with mild risk (< 10 % or patients over 80) they propose ultrasound of the abdomen and tumor marker assay every 6 months, endoscopy and chest X-ray annually, CT scan in case of clinical suspicion or increased level of tumor markers. For patients with moderate risk (between 10 and 50 %): tumor markers are investigated every 3 months, abdominal ultrasound after 6 months, 18 months, 30 months, and CT scan and endoscopy annually. For patients with high risk (> 50 %): tumor markers every 3 months, CT scan every 6 months, endoscopy annually.

After 5 years annual clinical monitoring, other exams if clinically indicated, any screening for second cancer (occult blood test, mammography, PSA, etc…)

To be noted that in international guidelines no nutritional or quality-of-life issues evaluation is considered.

By means of answering a questionnaire, a selected group of world-renowned experts in the field of surgical oncology were contacted via e-mail. The main portion of the survey focused on follow-up schedules and methodologies. Most questions were yes/no or multiple choice, with several text boxes included allowing for comments from participants to provide additional information or clarification.

All respondents reported having a strategy for surveillance after surgery for gastric cancer, but there was variance in strategy.

First of all we asked about the main reason for follow-up. For almost all respondents (4/6) the primary aim of the follow-up schedule is the evaluation of complications associated with surgery and quality-of-life issues and most of them perform nutritional assessment at visits. In one institution (University Hospital of Lille, France) the primary aim is the early detection of recurrence whereas in other institutions (Jagiellonian University, Krakow, Poland) it is the collection of outcome data for treatment evaluation and/or research purposes.

In 4/6 of responders follow-up schedule is carried out by a multidisciplinary team (surgeons with medical oncologists). In two institutions the follow-up is performed by the surgical team.

No significant differences were reported in terms of follow-up frequency for different disease stages. On average, advanced gastric cancer patients are followed-up every 3 months in the first year postoperatively, as opposed to follow-up every 6 months for early gastric cancer during the first year postoperatively. From the second to fourth postoperative year, the patients were usually seen every 6 months. In all cases follow-up ends at 5 years after surgery.

Table 19.3 summarizes the follow-up schedules as reported by respondents. Almost all respondents considered CT scan as mandatory for detection of all type of recurrence and PET scan as optional study.

One respondent left the question blank because he did not have a systematic follow-up schedule and performs advanced imaging and/or endoscopy during follow-up when symptoms arise or when there is clinical suspicion of recurrence.

Rationale for Follow-Up

Surveillance after surgery in gastric cancer includes three main purposes: detecting local or distant recurrences and or metachronous cancers in the remnant stomach; detecting long-term or late effects of surgical treatment; collection of outcome data to evaluate effectiveness of treatments and for research purpose.

Recurrence Patterns

The recurrence patterns of gastric cancer are classified as loco-regional, peritoneal, and hematogenous. Loco-regional recurrence is defined as cancer recurrence at the resection margin, within the lymph nodes (including regional, retropancreatic, retro-crural, and para-aortic nodes), or in the operation bed within the region of the resection (below the diaphragm and liver and

Table 19.3 Follow-up schedules

Institution	Months after resection													
	3	*6*	*9*	*12*	*15*	*18*	*21*	*24*	*30*	*36*	*42*	*48*	*54*	*60*
Memorial Sloan-Kettering Cancer Center, New York, USA	H&P exam	H&P exam, chest and abdominal CT, endoscopy, B_{12}		H&P exam, abdominal CT, endoscopy, B_{12}		H&P exam, abdominal CT, endoscopy		H&P exam, abdominal CT, endoscopy, B_{12}		H&P exam, abdominal CT, endoscopy, B_{12}		H&P exam, abdominal CT, endoscopy, B_{12}		H&P exam, abdominal CT, endoscopy, B_{12}
University Hospital of Lille, France	H&P exam, lab tests, chest and abdominal CT, CEA, CA 19.9, B_{12}, upper-GI x-ray	H&P exam, lab tests, chest and abdominal CT, CEA, CA 19.9, B_{12}, PET (optional)		H&P exam, lab tests, chest and abdominal CT, CEA, CA 19.9, B_{12}, endoscopy PET (optional)		H&P exam, lab tests, chest and abdominal CT, CEA, CA 19.9, B_{12}, PET (optional)		H&P exam, lab tests, chest and abdominal CT, CEA, CA 19.9, B_{12}, PET (optional)	H&P exam, lab tests, chest and abdominal CT, CEA, CA 19.9, B_{12}, PET (optional)	H&P exam, lab tests, chest and abdominal CT, CEA, CA 19.9, B_{12}, endoscopy PET (optional)	H&P exam, lab tests, chest and abdominal CT, CEA, CA 19.9, B_{12}, PET (optional)	H&P exam, lab tests, chest and abdominal CT, CEA, CA 19.9, B_{12}, PET (optional)	H&P exam, lab tests, chest and abdominal CT, CEA, CA 19.9, B_{12}, PET (optional)	H&P exam, lab tests, chest and abdominal CT, CEA, CA 19.9, B_{12}, endoscopy PET (optional)
Jagiellonian University, Krakow, Poland	Liver US, chest x-ray, endoscopy	Liver US, chest x-ray, endoscopy	Liver US, chest x-ray, endoscopy	Liver US, chest x-ray, endoscopy				Liver US, chest x-ray, endoscopy		Liver US, chest x-ray, endoscopy		Liver US, chest x-ray, endoscopy		Liver US, chest x-ray, endoscopy
Odette Cancer Research, Sunnybrook Research Institute, Toronto, Canada	H&P exam, lab tests, abdominal CT, CA 19.9, B_{12}, iron	H&P exam, lab tests, abdominal CT, CA 19.9, B_{12}, iron		H&P exam, lab tests, abdominal CT, CA 19.9, B_{12}, iron, endoscopy		H&P exam, lab tests, abdominal CT, CA 19.9, B_{12}, iron		H&P exam, lab tests, abdominal CT, CA 19.9, B_{12}, iron, endoscopy	H&P exam, lab tests, abdominal CT, CA 19.9, B_{12}, iron	H&P exam, lab tests, abdominal CT, CA 19.9, B_{12}, iron	H&P exam, lab tests, abdominal CT, CA 19.9, B_{12}, iron	H&P exam, lab tests, abdominal CT, CA 19.9, B_{12}, iron	H&P exam, lab tests, abdominal CT, CA 19.9, B_{12}, iron	H&P exam, lab tests, abdominal CT, CA 19.9, B_{12}, iron, endoscopy

Table 19.3 (continued)

Institution	Months after resection													
Leiden University Medical Center, the Netherlands	H&P exam,	H&P exam	H&P exam	H&P exam	H&P exam	H&P exam	H&P exam	H&P exam	H&P exam	H&P exam	H&P exam	H&P exam	H&P exam	H&P exam
Städtisches Klinikum Solingen, Germany	No Schedule													

H&P exam history and physical examination, *CT* computed tomography, *US* ultrasonography

above the pancreas and abdominal wound). In addition, the resection margin is divided into the proximal margin (including the lower third of the esophagus, remnant stomach, and gastrointestinal anastomosis) and the distal margin (duodenal stump). Peritoneal recurrence is defined as cancer recurrence in the abdominal cavity because of intraperitoneal distribution, including visceral metastasis and rectal shelf, peri-choledochal, and periureteral infiltration. Hematogenous recurrence has been defined as any metastatic lesion detected in distant organs [20, 21].

Timing of recurrence has been investigated by many authors and data are not uniform as reported. More than 90 % of patients relapse within 5 years after surgery, and 70 % relapse within 2–3 years [6, 7].

In early gastric cancer the rate of recurrence after gastrectomy is reported to vary from 1.3 to 12.2 %. Median time to recurrence is 16 months and hematogenous spread is probably the most common pattern of recurrence [22].

Many investigators have analyzed recurrence patterns, but the data have shown variable incidences of these patterns. This disagreement was attributed to differences in patient population, stage of the disease at the time of diagnosis, surgical treatment, and the mode and timing of recurrence detection. From literature review, in the West the pattern of recurrence tends to be local, whereas in the East the pattern is different, with more peritoneal and hematogenous recurrences [9].

Occasionally, after partial gastrectomy a second primary tumor can arise in the remnant stomach. Much of the literature relates to gastrectomies for peptic ulcer disease, which estimated a risk that is not so different from the general population [23, 24].

As regards gastric cancer, second primaries are more common after surgery for early gastric cancer because these patients have a good prognosis after curative surgery. The reported incidence of metachronous gastric cancer after partial gastrectomy for early gastric cancer is 0.6–3 % [25].

In clinical oncology practice, the detection of the recurrence in the early stage may provide an opportunity for effective treatment when patients are still fit enough to receive surgical or medical therapy.

Patients with gastric cancer recurrence are more often managed similarly to non-resectable patients because early detection of recurrence is quite difficult and peritoneal recurrence, one of the main patterns of recurrence, is usually diagnosed at an advanced stage.

With the possible exception of a few locoregional (anastomotic and lymph nodal) and hepatic metastases suitable of radical resection, the vast majority of recurrences are not surgically curable, and any resection is likely to be palliative or futile. Most patients with liver metastases are not candidates for resection and the survival rate after liver resection is very low and treatments for peritoneal metastases are still investigational [26, 27].

Chemotherapy is considered the mainstay in the treatment of recurrent gastric cancer and it is offered with the aim of improving survival and quality of life. Several randomized trials have indicated that patients with recurrent gastric cancer generally live longer when treated with chemotherapy than with optimal supportive care [28–30].

Recent advances in chemotherapy have achieved considerable tumor regression with median overall survival time reported between 6 and 13 months [17].

To date, these results notwithstanding, there is no clear evidence that treatment of a recurrence detected at an earlier stage improves outcome.

Long-Term and Late Effects After Gastrectomy

The follow-up is also important to evaluate the side effects of gastric surgery. Gastric resection leads to radical changes in the anatomy and physiology of the gastrointestinal tract and can cause severe nutritional complications. Any reconstruction technique must restore intestinal transit and ideally should provide good nutritional conditions for a good quality of life of patients.

Feeding problems occur in approximately 30 % of patients but severe symptoms are present

only in 1–2%. Symptoms can vary considerably and may be dependent on the individual susceptibility, comorbidities present prior to surgery, and the quality of the surgical procedures done. The main symptoms are early postprandial satiety, loss of appetite, alteration of taste, reflux, dyspepsia, nausea and/or vomiting, and diarrhea. Depending on type of surgery (total or subtotal gastrectomy) and reconstruction technique (BI, BII, or Roux) there are various "postgastrectomy syndromes" (Table 19.4). Gastric reservoir dysfunction (dumping syndromes), afferent and efferent loop syndromes, Roux-en-Y stasis syndrome, and bile reflux can lead to a reduction of food intake and occasionally to severe malnutrition [31].

Along with feeding concerns after gastric resection, regardless of the reconstruction technique, three metabolic and nutritional disorders may occur, including anemia, bone disease, and weight loss due to malabsorption.

Nearly 30% of patients present microcytic anemia (iron-deficiency anemia) or megaloblastic anemia (vitamin B_{12} deficiency). Iron deficiency is the most common anemia following gastric resection. After gastric resection both acid and pepsin, which are needed for iron absorption, are reduced. Moreover, owing to lack of intrinsic factor secretion, vitamin B_{12} deficiency is common after gastric resection mostly after total gastrectomy. Intramuscular injection of vitamin B_{12} every 3–4 months is recommended as a standard treatment for patients with vitamin B_{12} deficiency after total gastrectomy even if daily oral replacement therapy provides a safe and effective alternative treatment [32].

Changes in bone metabolism after gastrectomy have long been recognized. Gastrectomy has been identified as a risk factor for osteoporosis, osteopenia, and osteomalacia. The underlying mechanism of postgastrectomy bone disease is a combination of insufficient intake of calcium or vitamin D and lactose-containing foods, coupled with altered absorption, and metabolism. Calcium deficit increases calcium release from bone and impairs calcification of newly build bone matrix. Symptoms of osteoporosis may develop 10 or more years after gastric surgery because of the large amount of calcium that is normally stored in bone [33].

Table 19.4 Postgastrectomy syndromes

Postgastrectomy syndrome	Type of reconstruction	Symptoms	Treatment
Early dumping syndrome	>Billroth II	Within 30 min of eating: nausea, epigastric distress, diarrhea, vasomotor symptoms (dizziness, palpitations, flushing, diaphoresis)	Nonsurgical: diet changes—somatostatin analogs Surgery: conversion to Roux-en-Y or Billroth I and jejunal segment interposition
Late dumping syndrome	>Billroth II	1–4 h after eating: vasomotor symptoms	
Alkaline reflux gatritis	>Billroth II	Burning epigastric pain, nausea, bilious emesis	Nonsurgical: ursodeoxycholic acid Surgery: conversion to Roux-en-Y or Braun procedure
Roux stasis syndrome	Roux-en-Y in Distal Gastrectomy	Chronic abdominal pain, nausea, vomiting worsened by eating	Surgery: remove the atonic stomac
Afferent loop syndrome	Billroth II	First few weeks after surgery: severe abdominal pain and nonbilious emesis	Surgery
Efferent loop syndrome	Billroth II>Roux-en-Y>Billroth I	Months to years after surgery: abdominal pain and bilious emesis	Surgery
Post-vagotomy diarrhea	–	Diarrhea watery and episodic	Antidiarrheal medications
Nutritional disturbance	–	Anemia, neuropathy, dementia, osteomalacia	Supplementation

Weight loss is a frequent finding after gastric surgery. This occurs as a rule after gastrectomy, the lowest weight level is reached after 3–6 months. Most patients not having a relapse of the primary cancer show an increase of weight afterwards. After 12 months body weight is normally constant.

After hospital discharge, the principal cause of weight loss is a reduced caloric nutrient intake due to lack of appetite or complaints caused by abnormal passage. Factors that may cause malabsorption include the accelerate passage of large bolus in the jejunum, vagal denervation which increases the rapidity of the oro-cecal transit and bacterial overgrowth, due to decrease in gastric acid secretion, and pancreatic insufficiency [34, 35].

Follow-Up Armamentarium

The main components of surveillance strategy are: office visits for postoperative history and physical examination, blood tests especially tumor markers, imaging, and endoscopic studies.

There is no consensus regarding follow-up plan after gastrectomy for cancer and the optimum modality for the diagnosis of early recurrence is indeed unclear. Although there are many tools to detect recurrent disease in addiction to clinical examination (laboratory tests, imaging, and endoscopy), no one has high tumor specificity.

Laboratory Tests

Specific tumor markers are measured routinely to diagnose recurrence in an early phase because their positivity is easily measured with a simple blood test, but it is well known that they are not specific and cannot localize the recurrence site.

CEA and CA19-9 are known to be elevated in the serum of patients with advanced gastric cancer and a combination of CEA and CA19-9 monitoring has been used for the early detection of a recurrence after operation for advanced gastric cancer.

CEA and Ca 19-9 have a relatively good specificity profile (79–100 and 74–93.3 %, respectively), but a poor sensitivity profile (16–65.8 and 33.3–56 %) [36, 37].

Recent research showed that a combination of CEA and CA19-9 increased the sensitivity to detect recurrence to 85 %. In prospective studies, both tumor markers were useful indicators of recurrence, especially in patients in whom these markers are altered at preoperative stages, which are known to be the minority [38, 39].

In prospective studies, both tumor markers were useful indicators of recurrence, especially in almost all those patients who showed high preoperative levels of these markers [38, 39].

CA19-9 may be especially useful as a marker for peritoneal recurrence of the gastric cancer, and CEA for recurrence in the liver [40].

Other tumor markers, such as CA 72-4 and CA 125, have been investigated, but their sensitivity is significantly lower than that for CEA and CA19-9 [41].

Imaging

Reports on the use of imaging in detecting recurrent gastric cancer are few, and are often limited to descriptions of typical findings.

Contrast-enhanced abdominal computed tomography (CT) is used most frequently and is regarded as the most reliable method for assessing cancer recurrence, with a reported accuracy of 60–70 % [14].

To date, however, only few reports have been published on CT findings after gastrectomy. CT scan has a limited value in the distinction of postoperative morphologic changes from tumor recurrence and has a low positive predictive value to detect peritoneal and distant lymph node metastasis [42].

Positron emission tomography (PET) is often useful for detecting different patterns of recurrence, such as local recurrence involving the stomach remnant, regional lymph nodes, peritoneal dissemination (Fig. 19.1), liver metastases (Fig. 19.2), and remote metastases (Fig. 19.3). This modality has a sensitivity of 89.7 % and a

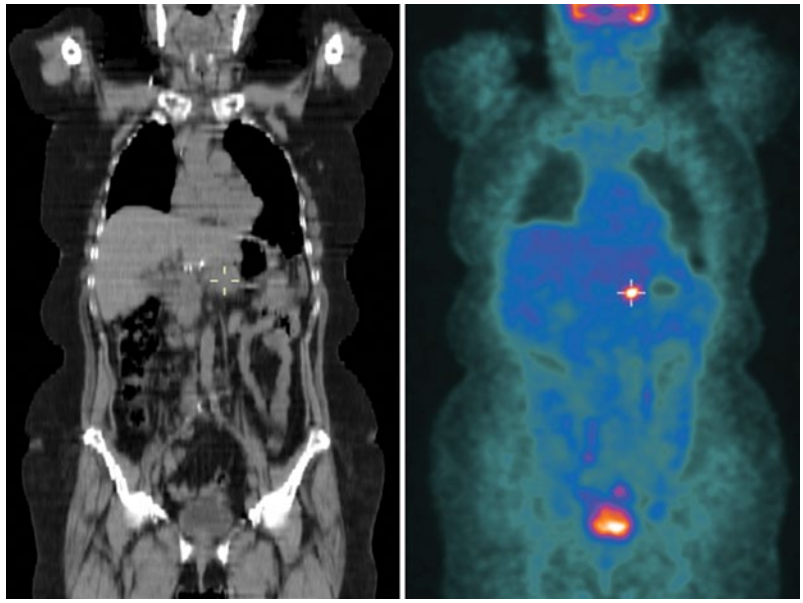

Fig. 19.1 ^{8}F-FDG PET/CT scan showing uptake near the stomach remnant 18 months after subtotal gastrectomy for locally advanced gastric cancer (pT3N1M0). Surgical exploration revealed localized peritoneal carcinomatosis

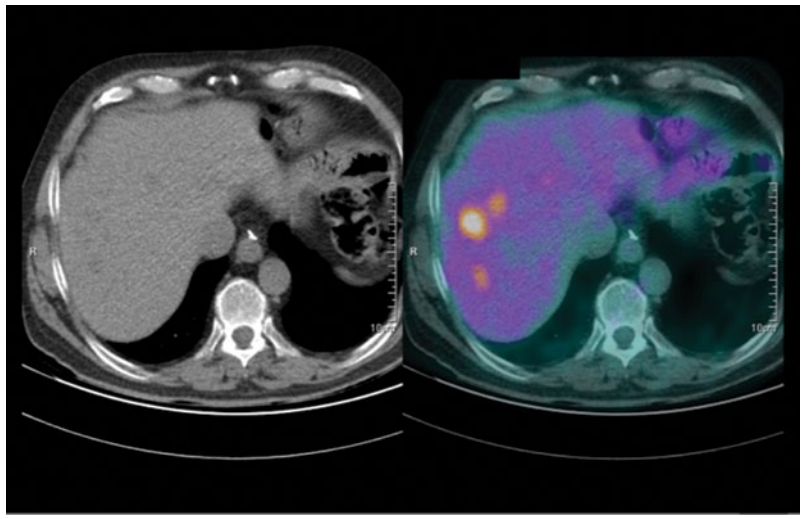

Fig. 19.2 ^{8}F-FDG PET/CT scan showing three liver metastases 12 months after subtotal gastrectomy for locally advanced gastric cancer (pT3N0)

specificity of 85.7% in detecting distant and local recurrences. PET is an advantageous imaging tool because it enables the evaluation of the entire body at once even if PET has also limitations such as frequent false-negative cases, either in early cancer or in signet-ring cell tumor or poorly differentiated histotype. PET study is useful when conventional imaging is equivocal, as it can confirm the presence of true recurrence [43].

PET represents the most useful noninvasive imaging modality for the detection of hepatic metastases from gastric cancer with a sensitivity of

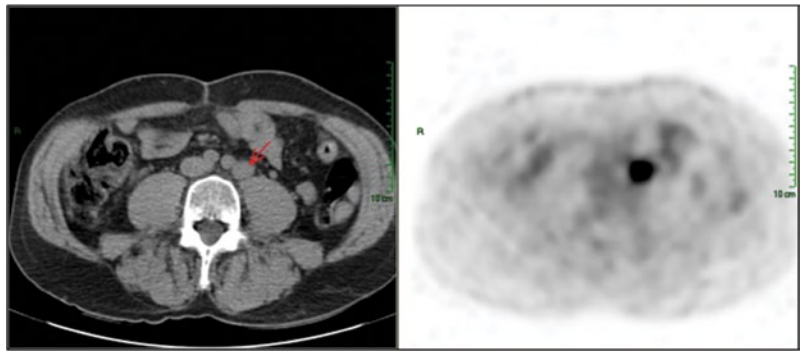

Fig. 19.3 Gastric cancer recurrence 36 months after total gastrectomy for locally advanced gastric cancer (pT-2N2M0) in a single para-aortic lymph node well depicted in the CT scan (*red arrow*), and revealing ^{8}F-FDG uptake in the PET scan

90% compared with a sensitivity of 76, 72, and 55% reported for magnetic resonance imaging, CT, and ultrasonography, respectively [44–46].

Integrated PET/CT scan provides fusion images, combining functional and anatomic imaging together. This modality has a diagnostic accuracy ranging from 75 to 97%. PET/TC scan has the greatest utility in the patients with a suspicion of recurrences based upon tumor markers test and on the findings of other imaging modalities [47–49]. A recent multicenter Italian study examined the efficacy of follow-up investigations for recurrence diagnosis in 814 patients who have developed a recurrence after gastric resection for cancer. From their data only CT scan and 18-FDGPET could identify more than 90% of recurrences (93.6 and 91.0%, respectively) [50].

All imaging studies have low accuracy in detecting peritoneal disease which represents one of the most frequent and feared pattern of recurrence. Barium enema has been used in the diagnosis of peritoneal carcinomatosis in colorectal cancer [51], and this imaging has been used in Japanese institutions to confirm the presence of peritoneal disease, when clinically suspected [9].

A recent study by Inoue et al. evaluated the feasibility and accuracy of second-look laparoscopy for patients with gastric cancer at high risk of peritoneal recurrence after completion of 6-months of systemic adjuvant chemotherapy. In this study, second-look laparoscopy was a safe and effective approach to early reassessment of peritoneal disease selecting patients who needed further systemic chemotherapy [52].

Endoscopy

The use of endoscopy during the follow-up period is recommended, for the risk of recurrence in the stomach remnant, in two cases: after a subtotal gastrectomy and after endoscopic treatment for early gastric cancer. After total gastrectomy endoscopy is mostly useful to detect surgical complication, like benign stricture [53].

Lifelong annual follow-up endoscopy is recommended after partial gastrectomy. Two-thirds of the patients destined to develop a second primary gastric cancer will show sign of disease within 10 years after surgery. The risk is higher in patients with multiple lesions at initial surgery and in patients with undifferentiated-type carcinoma [54].

Careful endoscopic examination of the entire stump, particularly around the lesser curvature and posterior wall, is essential. Elevated and depressed mucosal changes should be examined histologically. Follow-up endoscopy seems important for the early diagnosis of second primary. When detected at early stage treatment provides excellent disease-free survival. However, when second primary is detected at a later stage (≥T2) the prognosis is poor even after curative resection [55–57].

After endoscopic treatment by submucosal dissection of early gastric cancer, patients are at high risk for synchronous or metachronous multiple gastric cancers. Large multicenter retrospective cohort study indicated that the incidence rate of synchronous cancer was 9%, that about 20% of synchronous cancers were missed and that the annual incidence of metachronous cancer was 3.5%. With an annual follow-up examination, almost all multiple lesions could be treated by endoscopic resection [58].

Conclusion

The reported international variation in guidelines for surveillance among follow-up schedules reflects a complete lack of established evidences. Consequently, most recommendations aiming to detect early recurrence of the disease, more often avoid details on the mode, duration, and intensity of surveillance, since they cannot be based on studies with high level of evidence. Moreover, quality-of-life issues are omitted in current literature on surveillance, even if most experts underline the importance of this peculiar subject especially after total gastrectomy.

On the other hand, there is almost no doubt that from most patients' and physicians' perspective a good clinical practice should not disregard some kind of postoperative surveillance, but from literature review and expert interviews we found that routine follow-up of gastric cancer patients is nothing more than a common behavior, that is at least justified by data collection and outcome auditing, besides ethical–psychological reasons concerning the anxiety of patients regarding full and prompt information about the evolution of their disease.

Although retrospective series have clearly demonstrated that early diagnosis of tumor recurrence in the asymptomatic phase has not resulted in any evident survival benefit compared to a later symptom-driven diagnosis, the majority of the centers with a considerable gastric cancer case-load and high level of care apply a policy of clinical and instrumental surveillance with the aim to lead to a timely diagnosis of tumor recurrence and to minimize the nutritional sequelae of gastrectomy.

To date it is certainly needed that follow-up schedules are founded on more solid ground, by identifying those tests and examinations with the best reliability and sensitivity and by limiting them to a period in which recurrence is likely.

Surgical oncologists could speculate that patients may receive some benefit by postoperative surgical surveillance if early detection of recurrence leads to any proven survival advantage and/or increased quality of life. Whether there is a preclinical phase in which early detection of recurrence can improve outcome (implying that followed-up patients may have better overall outcomes than unscreened) represents a question apparently suitable for a randomized controlled trial, which is commonly considered as the most rigorous method of determining if a cause–effect relationship exists between an intervention and its outcome [59]. Although a large randomized trial could determine whether one recommended follow-up program confers survival benefit, this is unlikely to be rewarding until effective treatments for most patterns of recurrence will be available. In fact, at the moment, in high-risk patients clinical trials on the efficacy of surveillance strategies will be doomed to show no efficacy if survival is their primary endpoint, because survival after recurrence is poor regardless of the time of diagnosis. At the same time, follow-up strategies in low-risk patients with good long-term prognosis (i.e., early gastric cancer) necessitate an excessively long time to demonstrate clear improvements in outcome. In both cases, huge sample sizes, money, and time are almost insurmountable obstacles.

Consensus methods are alternative means of dealing with conflicting or scarce scientific evidence. The focus of consensus methods lies where unanimity of opinion does not exist, owing to a lack of scientific evidence or when there is contradictory evidence over an issue. Consensus methods overcome some of the disadvantages normally found with decision making in groups or committees, which are commonly dominated by one individual or by coalitions. The consensus method attempts to assess the extent of

agreement and to resolve disagreement [60]. Currently, in our opinion, an appropriately designed and methodologically founded consensus conference may be a proper tool to establish the best way to adequately perform follow-up in gastric cancer patients.

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Surgical Trials for Gastric Cancer

20

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Despite recent advances in multimodal treatment concepts for gastric cancer, surgery remains the mainstay of therapy for this often fatal disease. Therefore, adequate oncologic resection is of utmost importance to the patient in order to improve survival and quality of life (QoL). Not only the radicality of lymph node dissection but also the reduction of surgical trauma to reduce the immunologic reactions is considered to be crucial, which may be detrimental for the patient's oncologic outcome.

Several trials have been conducted over the recent years investigating on the relevant issues of lymph node dissection, the role of laparoscopic surgery, and new technical developments. This chapter covers the developments of the most important trials that have been conducted in the past and provides an outlook into the future.

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Extent of Lymph Node Dissection

In order to understand the different philosophies for lymph node dissection between Eastern Asian and Western surgeons, one has to review the existing data critically. The reservations on D2 lymphadenectomy by European and US Americans are mostly based on data derived from so far six randomized controlled trials (RCTs), which compared D1 to D2 lymphadenectomy [1–8]. Five of those originated from the Western hemisphere. The outcomes of these trials have been reported extensively before. The first trial by Dent et al. revealed superiority for D1 lymph node dissection regarding hospital stay, morbidity, and number of blood transfusions whereas hospital mortality and overall survival were comparable between the groups [1]. Another trial by Robertson et al. compared D1 subtotal gastrectomy to D3 total gastrectomy with pancreaticosplenectomy in a small cohort consisting of 55 patients and concluded that survival was significantly improved in the D1 group [8]. One of the two most important trials was the Dutch Gastric Cancer Group randomized controlled trial comparing D1 vs. D2 lymphadenctomy in gastric cancer patients [7]. This trial included 711 patients who underwent D1 or D2 lymph node dissection after randomization. Conclusively, patients undergoing D2 dissection revealed a significantly higher morbidity (43 vs. 25 %, $p < 0.0001$) and mortality rate (10 vs. 4 %, $p = 0.004$). The high morbidity and mortality rate was later attributed to the fact that most of the patients received either distal pancreatectomy

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and/or splenectomy. Long-term follow-up data were published for 11 and 15 years of follow-up and demonstrated no significant differences in overall survival, but cancer related death was significantly lower in the D2 group (37 vs. 48%, $p=0.01$). This might be attributable to the fact that in case of surviving the immediate postoperative course after D2 dissection, a benefit in overall survival for the respective patient is postulated [9]. This fact led to the general recommendation in Western guidelines to accept D2 lymphadenectomy with preservation of the pancreatic tail and spleen as standard of care, if oncologic surgery is performed in specialized centers. Another major trial was the Medical Research Council trial investigating on the same outcome after including 400 patients [2]. Here, increased morbidity and mortality was demonstrated as well: 46 vs. 28% ($p<0.001$) morbidity in favor of D1 and 13% vs. 6.5 ($p=0.04$) mortality with the lower rate for D1 as well. Five-year survival rate was reported comparable between D1 and D2 dissection (33% in D1 and 35% in D2-resected patients). The absence of detectable benefit of D2 dissection was attributed to the fact that pancreaticosplenectomy was performed in 56% of the D2-resected patients compared to 4% in the D1 group, explaining the higher morbidity and mortality rate. The interims analysis of the Italian Gastric Cancer Study Group trial by Degiuli et al. demonstrated for the first time that D2 dissection is safe and feasible when the pancreas is being preserved [3–5]. Compared to the former trials, surgical morbidity and mortality could be decreased to 16.7 and 3.1% in the D2-dissected group, when specialized surgeons performed the surgical procedure. Nonetheless, the final results of this trial do not support a general applicability of D2 dissection. The subgroup analysis in the Italian trial demonstrated that possibly patients with advanced cancer benefit from D2 dissection. However, this trial revealed for the first time an impressive 5-year overall survival rate of 65%, which is higher than in any other published European trial. In this specific group a significant survival benefit was noted. Eastern Asian trials are not available to date, as D1 dissection is not considered an option of treatment due to the Maruyama data from the late 1980s. There is one Taiwanese prospective randomized trial comparing D1 to D3 gastrectomy, showing significantly higher 5-year disease specific survival rates in patients having undergone extended dissection (D3): 59.5 vs. 53.6% $p=0.041$ with a significantly reduced recurrence rate after R0 resection of 40.3% in D3 vs. 50.6% in the D1 group [6]. Those trials have been reviewed in a meta-analysis summarizing 1876 patients treated in those six randomized controlled studies [10]. In total 946 patients were allocated to D1 dissection compared to 930 patients in the D2 group. The relevant results were that D1 lymphadenectomy was in favor of shorter hospital stay (6.37 days difference, $p=0.0036$), 58% less postoperative complications ($p=0.0002$), 60% less anastomotic leakages ($p<0.0001$), 67% less reoperation rate ($p=0.006$), and 41% less 30-day mortality rate ($p=0.0054$). Finally no difference in 5-year survival rate could be shown ($p=0.7662$). The conclusion based on these data was that "best clinical evidence comparing D1 and D2 surgery does not favor the D2 resection." Another meta-analysis omitting the Dent et al. trial from Brazil [11] comes to the same conclusion, having reported less postoperative morbidity and mortality as well as shorter hospital stay in the D1 group. They found significantly lower local recurrence rates for the D2/D3 group ($p=0.02$) and lower mortality for patients with recurrent disease ($p=0.04$). Nonetheless, statistical benefit for the 5-year survival rates could not be noted ($p=0.40$). Data from retrospectively analyzed patient cohorts ($n=1904$) revealed a trend toward survival benefit for D2 dissection in T3+ tumors but found no statistical significant improvement in 5-year survival ($p=0.10$) [12]. Conclusively one has to state that all RCTs and meta-analysis of those trials failed to demonstrate survival benefits in D2-dissected patients. However, experience from Korea and Japan demonstrates the opposite trend.

Extended Lymph Node Dissection: D2+Paraortic Node Dissection (PAND)

As D1 dissection is considered not adequate for the treatment of Eastern Asian patients, RCTs have been performed in order to evaluate an even more radical lymph node dissection. The most

important study was published by the Japanese Clinical Oncology Group, comparing D2 dissection to D2 dissection accompanied by paraaortic node dissection (PAND) in 523 patients, concluding that surgery-related complications were statistically significantly higher in the D2+PAND group (28.1 vs. 20.9%, $p=0.07$) without benefit in recurrence free and 5-year overall survival ($p=0.85$) [13]. Another multicenter trial performed in Japan, Korea, and Taiwan confirmed those results [14]. Interestingly, preliminary data from a Polish randomized controlled trial demonstrated no difference in postoperative complication rate in 275 randomized patients [15]. Survival data from this RCT are being awaited eagerly. A meta-analysis from 2010 [16] on four RCTs with a total of 1120 patients revealed no statistically significant difference in 5-year survival ($p=0.55$). Interestingly, a benefit in 5-year survival was detected for the serosa-negative subgroup, when D2+PAND was performed ($p=0.04$). In serosa-positive tumors only the Sasako study was included and revealed advantages for the D2 only group ($p=0.02$). All other outcomes revealed less operation time ($p<0.0001$) and less blood loss ($p<0.0001$) in the D2-only group whereas postoperative morbidity and mortality were comparable ($p=0.98$). The authors concluded that D2+PAND dissection can be performed safely, but failed to demonstrate survival benefits. Long-term analyses and results are expected, which might even change the value of D2+PAND dissection.

Conclusions Drawn from the Western Trials

European surgeons will have to ask the question, "Why Western trials have failed to demonstrate survival benefits, although performed in a highly sophisticated setting?" In the Dutch randomized controlled trial, training sessions were performed together with experienced surgeons from Eastern Asia [7]. Those experts were even attending the first surgeries performed in these trials and gave their valuable input in order to guarantee quality in this trial. One major aspect might be that the case load in European centers, even in experienced ones, is still low compared to Korean or Japanese hospitals and, thus, surgical skills and abilities in the D2 procedure are underrepresented in European hands. Other reason might be that European patients themselves differ in their attributes from Eastern Asian patients. Adiposity is an important issue in Western countries derived from high-calorie food intake. Furthermore, adiposity-related comorbidities are far more common in Western patients than in Korean or Japanese. Diabetes, severe coronary heart disease, peripheral vascular disease, and metabolic syndromes are overrepresented in Europe and especially in the USA [17]. Those comorbidities might have influenced the trial outcomes in a way that has not been evaluated so far. Identification of the respective lymph node stations may be difficult due to excessive visceral fat, so that noncompliance to the respective treatment protocol within the respective trial appears to be more probable. The experience from the Dutch trial reported 84% noncompliance with the protocol, rendering interpretation of the study result difficult [18]. Furthermore, in light of those results, proper N staging might not have been correct, as stage migration occurs when the number of lymph nodes retrieved increases [19]. The stage-adopted results might thus be not directly comparable to Eastern Asian collectives. Besides these facts, the Dutch trial reported only 66% of surgeries with curative intent [18]. In Eastern Asian patients, surgery is mostly performed on patients with early gastric cancer due to nationwide screening programs and early detection [20, 21]. Screening programs are not recommended in Western guidelines, as benefit is not related to the cost of a nationwide screening program [22]. That is why, most patients present at a stage when the tumor has progressed and become symptomatic, leading to disease-related weight loss and cachexia. This indicates that Western patients' fitness for surgery due to progressive disease and patient comorbidity might be much less pronounced compared to Eastern Asian ones.

The issue of D2 dissection in patients with gastric cancer remains controversial at least in Europe. Meta-analyses on prospective RCTs

revealed no statistical survival benefit for European patients undergoing D2 dissection. Several groups were able to show that D2 dissection is safe and feasible without increased risk for the patient, if the pancreas and spleen are being preserved during the operative procedure. However, 15-year follow-up data revealed significant improvement of postoperative survival for gastric cancer patients undergoing D2 dissection [9]. The Eastern Asian experience shows that high volume surgery and stringent adherence to D2 dissection in experienced hands lead to markedly improved survival compared to Western data. Prospective trials on even more extended lymph node dissection (D2+) did not yield survival benefits. Conclusively, D2 dissection with pancreas and spleen preservation should be recommended in Western patients, when surgery is being performed in Western centers with adequate case load and experience.

Role of Prophylactic Bursectomy and Splenectomy

Bursectomy is a procedure dissecting the peritoneal lining covering the pancreas and the anterior plane of the transverse mesocolon, and has been proposed as an additional procedure for radical gastrectomy in advanced gastric cancer. Imamura and colleagues from Japan investigated on the postoperative morbidity and mortality in an RCT randomizing 210 patients. The authors identified an increase of intraoperative blood loss as the only significantly different factor. Major complications such as anastomotic leakage, pancreatic fistula, abdominal abscess formation, and mortality did not differ between the two groups. Therefore, the authors concluded that bursectomy is a safe procedure [23]. Interim analysis of the same trial on 3-year overall survival demonstrated some survival benefits, especially in patients with serosa-positive cancers. However, these results were not statistically significant. Therefore, bursectomy may not be recommended as a standard procedure for serosa-positive cancers to date [24].

The role of prophylactic splenectomy in order to appropriately remove the number 10 lymph nodes was investigated in a Korean RCT. Yu et al. randomized 207 patients undergoing gastrectomy for proximal gastric cancer. In this trial, splenectomy did not improve postoperative overall survival in the patients receiving prophylactic splenectomy [25]. Another trial from Japan was conducted on 500 patients, but results are not available yet (Sasako M, JCOG0110, NCT00112099). Therefore, prophylactic splenectomy may not be recommended to date.

Sentinel Lymph Node Concept

Despite the fact that Eastern Asian surgeons adhere to extensive lymph node dissection, numerous efforts were undertaken to evaluate the role of the sentinel lymph node concept in early gastric cancer patients, who are not suitable for endoscopic resection. The sentinel node concept was investigated in for malignant melanoma and breast cancer and has become a standardized procedure to reduce surgical trauma. All patients with more than pT1b sm1 infiltration depth are exposed to a risk of lymph node metastasis, which is reported to be up to 25 %. Several Eastern Asian surgeons therefore addressed the concept of identifying a sentinel lymph node, which might provide more information on possible lymph node spread and improve surgical outcomes by reduction of postoperative complications. The most demanding challenge so far is the oncologic safety. Several retrospective analyses demonstrated feasibility and safety of sentinel node detection. However, only two prospective trials were published over the recent time revealing conflicting results.

The first trial reported by Miyashiro et al. from Japan demonstrated a high false-negative proportion of the intraoperative histological examination of the sentinel node in patients with T1 gastric cancer [26]. The primary endpoint of this prospective trial was to evaluate the feasibility and accuracy of sentinel lymph node biopsy. In this trial the sentinel node was detected by indocyanine green (ICG) staining. The node was dissected and analyzed. Afterward, all included patients were subjected to standardized lymph node dissection. All participating institutions

passed a training period in order to gain technical experience with the procedure. The sentinel node detection rate by ICG injection was almost 98%. However, the trial was stopped preliminary because of a high false-negative rate of 46% according to recommendations of the safety and monitoring board. The authors concluded that biopsy of a single sentinel node cannot be considered a safe procedure to rule out lymphatic metastasis. The authors further stated that reasons for this were discrepancies between frozen and paraffin sections, the short learning period of only five patients, and the surgeon's inexperience with the procedure.

Another prospective study was again performed by Japanese surgeons. Kitagawa et al. published a multicenter phase II study to demonstrate safety of sentinel node mapping by using a dual tracer endoscopic injection technique [27]. In this trial the sentinel mapping procedure differed from the Myashiro study. Here, a dual sentinel mapping procedure was performed using a Tc99m-labeled colloid and additionally injecting isosulfan blue dye around the tumor area in the stomach. The sentinel detection rate was 97.5%. The diagnostic accuracy was calculated at 99% and the false-negative rate was 7%. The authors concluded that sentinel mapping may be considered safe and feasible and is even comparable to data from melanoma and breast cancer trials. The authors stated further that more advanced cancers (>cT1) are not suitable for this procedure, because the false-negative rate was significantly higher in more advanced gastric cancer patients.

The results of these trials stand in stark contrast. Differences may be related to the different sentinel mapping methods and the limited training period in the first trial. Whereas the training period for the procedure in the Kitagawa trial was 30 patients, the technique was practiced only in five patients in the Myashiro trial. Further studies investigating the concept of the sentinel technique introduced an extensive training period in which the procedure is evaluated by independent reviewers before trialists receive approval to continue with the study. The recently initiated SENORITA trial from Korea (NCT01804998) incorporates a quality control study of the sentinel node biopsy. All 15 trial centers have to complete a training period and fulfill specific requirements before participation in the trial is approved. The SENORITA trial is a multicenter phase III RCT enrolling 580 patients. The trial intervention is different from the so far published Japanese trials. Here, sentinel node basin is dissected in order to reduce the rate of false-negative biopsy. After ruling out lymphatic metastases, the primary tumor is removed by wedge resection. This trial is the first to treat patients with early gastric cancer by sentinel node mapping and stomach preserving surgery on a large scale and will be the landmark trial approving or rejecting this concept of treatment in early gastric cancer, which is not suitable for endoscopic resection. The primary endpoint of this trial is the 3-year overall survival. Short-term results on postoperative outcomes are going to be expected in 2017.

Conclusively, the data on sentinel lymph node dissection cannot be translated into clinical practice yet. The data on the two prospective trials from Japan are contradictory. Further, oncologic safety has not been proven yet in a randomized controlled phase III trial. Probably the results of the SENORITA trial may elucidate that matter in the future. Also, the role of sentinel node dissection and stomach preserving surgery in the Western hemisphere will have to be validated before incorporation into clinical practice.

Minimal Invasive Surgery

Since the first publication of laparoscopy-assisted gastrectomy by Kitano in 1994 [28], numerous efforts were undertaken to introduce minimal invasive surgery into clinical practice. Again the drivers of this movement originated from Korea and Japan. Due to the high rate of early gastric cancers, which are detected by the national screening programs, less invasive treatment methods were established. Numerous retrospective analyses, which showed potential benefits such as shorter hospital stay, less postoperative pain, and less overall morbidity, were published over the past 20 years. However, prospectively RCTs have been undertaken only since the last decade.

The first randomized study comparing open to laparoscopic surgery for gastric cancer patients was published by the pioneer of minimal invasive gastric cancer surgery in 2002 [29]. In this trial, 28 patients were randomized into groups either undergoing open or laparoscopic-assisted distal gastrectomy. The results demonstrated better pain control, less blood loss, earlier bowel recovery, and less impaired pulmonary function. Another prospective trial from Korea revealed similar results in 47 seven early gastric cancer patients [30]. The authors further reported 14-month follow-up, which revealed no statistical differences in survival. The first prospective study on the evaluation of laparoscopic surgery from Europe was published by Huscher et al. [31]. Here a total of 59 patients were randomized. Interestingly, not only patients with early gastric cancer but also advanced gastric cancer patients were included in this RCT. The 5-year overall survival did not differ between the open and the laparoscopic groups. In addition, there was no statistically significant difference in lymph node retrieval. Therefore, the authors concluded that laparoscopic distal gastrectomy was an oncologically safe procedure. The first trial reporting on QoL after open or laparoscopic gastrectomy was conducted in Korea [32]. Here, 164 patients were randomized between 2003 and 2005. The authors found that minimal invasive distal gastrectomy was not only beneficial related to intraoperative blood loss, reduced amount of analgesics, and postoperative hospital stay but also in terms of QoL. The trialists demonstrated significant improvements for fatigue, chronic pain, emotional/social/symptom scales, appetite loss, sleep disturbances, dietary restrictions, anxiety, and body image, when patients were subjected to the laparoscopic approach. The long-term results of this RCT revealed excellent survival data without statistically significant differences (5-year disease free survival: 98.8 % (laparoscopic approach) vs. 97.6 % (open approach), $p = 0.514$). However, the short-term benefits in QoL were not reproducible after the end of the follow-up period [33]. The first multicenter phase III trial was reported from Korea in 2010 [34]. This study reported an interims analysis on safety of the largest cohort to this date. In total, 342 patients with preoperative stage I gastric cancers were enrolled from 13 centers all over Korea. The interim evaluation demonstrated no differences in morbidity and mortality between the open and laparoscopic groups. Therefore, the trial was continued until full recruitment of 1416 patients. The final results of this trial are expected to be published in the near future. Interestingly, Japanese surgeons did not publish a phase III trial on the impact of laparoscopic surgery for early gastric cancer yet. However, the JCOG0912 trial, which finished enrollment of 920 patients from 33 centers in Japan, is momentarily in the follow-up period. Results may not be expected before 2017 [35].

The first prospective study reporting of laparoscopic surgery in exclusively advanced gastric cancer patients was published by a Chinese group [36]. This RCT randomized 123 patients into either an open or a laparoscopic approach. The authors found significantly longer operating times and significantly less pulmonary infections in the laparoscopic group without compromising oncologic safety. Another prospective phase II study on the evaluation of laparoscopic surgery from Korea reported on 204 patients having been treated between 2008 and 2012. This study included patients with cT2N0 to cT3N2 staged gastric cancer. Conversion to open surgery was necessary in 7 % of the cases. Mean hospital stay ranged from 6 to 9 days depending on the type of surgery (distal gastrectomy or total gastrectomy). The number of retrieved lymph nodes was 52 in the distal gastrectomy group and 64 in the total gastrectomy group, implying adequate oncologic safety. The complication rate according to the Clavien-Dindo classification was acceptable ranging from 3 to 8 %. The authors therefore concluded that laparoscopic surgery for advanced gastric cancer may be considered safe and feasible [37].

Based on the implications of the above-mentioned trials, future trials are going to evaluate the outcome of laparoscopic surgery in advanced gastric cancer patients on a large scale. The Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) Group launched a large-scale prospective study randomizing an estimated 1050 patients in 11 centers all over Korea for pa-

tients being treated for cT2 to cT4a N+/− distal gastric cancer since 2012 (NCT01283893). Primary endpoint is the 3-year overall survival. In order to ensure surgical proficiency, every participating surgeon has to participate in a quality control study similarly to the above-mentioned SENORITA trial. Potential contributors have to submit a defined number of unedited videos to an independent reviewer committee, which evaluates the proficiency with the procedure. Only when the review board approves the submitted videos the applicant may proceed with the phase III study. This procedure underlines the importance of adequate surgical skills in surgical trials and further demonstrates the awareness of the trialists to ensure safety for the respective patient. The Japanese Laparoscopic Surgery Study Group also launched a combined phase II/phase III trial on laparoscopic surgery for advanced stage distal gastric cancer in 2010 with a target sample size of 500 patients (JLSSG0901: Adv.GC-LAP/OPEN, PII/III, JPRN-UMIN000003420). The primary endpoint for phase II is pancreatic fistula and for phase III relapse-free survival.

An unresolved issue is the feasibility of laparoscopic surgery in patients having undergone preoperative/neoadjuvant chemotherapy for locally advanced gastric cancer. So far, no reliable data are available. This is an important issue for patients in the Western hemisphere, as neoadjuvant or perioperative chemotherapy is considered a standard of care for advanced gastric malignancies. The LANDSCOPE trial from Japan is going to evaluate safety and feasibility for those patients [38]. This phase II trial recruited 80 patients with cT4a cN0-3 distal gastric cancer having received neoadjuvant chemotherapy with the primary endpoint of 3-year overall survival rate. The only European STOMACH-trial is supposed to be initiated in the near future. However, specific data on the design and rationale are not available yet.

Almost all of the above-mentioned trials deal with gastric malignancy in the distal part of the stomach. However, the impact of laparoscopic surgery for total gastrectomy has not been evaluated yet within RCTs. So far, there is only one registered trial from Korea investigating safety and efficacy of laparoscopic total gastrectomy for early gastric cancer (KLASS-03, NCT01584336). The primary endpoint is the incidence of postoperative morbidity and mortality. The role of total gastrectomy for advanced gastric cancer remains completely elusive to the current date.

Conclusively, there is convincing data derived from prospectively RCTs on the applicability of laparoscopic surgery for early gastric cancer patients. The role of laparoscopic approaches for total gastrectomy and advanced gastric cancers remains elusive until final publication of many promising trials in Eastern Asia. However, it appears to be questionable if those results may be transferred to patients in the Western hemisphere. Further, there is a complete lack of data for laparoscopic treatment of gastric cancer located at the gastroesophageal junction, which is the primary location in European and American patients.

Robot Surgery

Robot-assisted surgery is an enabling new technique that is supposed to overcome the drawbacks of conventional laparoscopic surgery by incorporating 3D visualization, increased range of movement abilities, and omission of natural tremor transduced to the instruments. Several retrospective analyses investigated on the applicability of the most commonly used DaVinci robotic system for gastric cancer surgery. However, the conduct of RCTs represents a demanding effort. In Eastern Asia there is a substantial problem to randomize patients due to the local health care system in which potential patients have to pay for the robotic system by themselves. In the Western hemisphere, accrual of patients into trials is strenuous due to the constantly decreasing incidence of gastric cancers. The International Clinical Trials Registry Platform from WHO lists nine phase II trials evaluating the role of robot-assisted gastrectomy. The largest study is a prospective multi-institutional registry with a target size of 1700 patients (NCT01309256). A rela-

tively large phase II trial from Japan evaluates the incidence of postoperative intra-abdominal infectious complications (anastomotic leakage, pancreas related infection, and intra-abdominal abscess) as a primary endpoint since 2012. Phase III trials are not registered in any of the trials databases yet.

Non-curative Surgery for Metastatic Gastric Cancer

New developments in multimodal treatments for gastric cancer, especially new chemotherapeutic and biologic compounds, led to dramatic improvements in tumor response. Therefore, the possibilities of noncurative surgery have increased over the recent years. The role of noncurative gastrectomy, completely regressive metastatic disease, and debulking surgery for peritoneal seeding, followed by intraperitoneal chemotherapy have opened up new fields of clinical research demanding randomize controlled trials.

Treatment of Gastric Cancer with Intraperitoneal Antitumor Agents

Gastric cancer frequently spreads via the peritoneal route and the peritoneum is also a common site of tumor recurrence. The peritoneum–plasma barrier makes the administration of rather high dosages of hydrophilic anticancer drugs possible, since the peritoneal permeability is usually lower than the plasma clearance of the same agents [39]. Due to the reduced permeability into the plasma, systemic concentrations of these substances are lower, which results in lower toxicity [40]. The direct route of administering antitumor agents is therefore appealing in gastric cancer with peritoneal spread. Numerous trials investigated the intraperitoneal (i.p.) route of administration of normo- and hyperthermic cytotoxic substances and antibodies in conjunction with or without cytoreductive surgery, and there are some interesting ongoing trials in this field that are summarized in the following sections.

Intraperitoneal Chemotherapy

Based on the promising results in ovarian cancer [41], the presently ongoing Japanese INPACT trial is investigating i.p. paclitaxel vs. i.v. administration of the same drug in gastric cancer patients considered at high risk for developing peritoneal carcinomatosis (macroscopic type 3 gastric cancer > 8 cm or type 4 or another macroscopic type highly suspicious for serosal invasion or peritoneal seeding) in a phase II setting [42]. I.p. chemotherapy is administered via an i.p. reservoir in a dose of 60 mg/m2 paclitaxel on the day of surgery and days 15, 22, 29, 43, 50 and 57. In the i.v. arm, paclitaxel is given in a dose of 80 mg/m2 on the same days. After 2–3 weeks, both regimens of treatments are followed by systemic chemotherapy for advanced gastric cancer (S-1 monotherapy or S-1 and cisplatin), which is a standard in Asia. The primary endpoint of the study is 2-year overall survival (OS) rate. Secondary endpoints are the incidence of adverse events, progression-free survival time, and overall survival time.

Kuramoto et al. investigated the combination of extensive peritoneal lavage (EIPL) with i.p. chemotherapy in an RCT including 88 patients with gastric cancer and cytologic-positive peritoneal lavage fluid but no macroscopic peritoneal dissemination (CY+/P−) [43]. EIPL was performed with 10 × 1 l of saline. Cisplatin was administered i.p. in a dose of 100 mg/kgBW in 500 ml of saline after surgery or surgery + EIPL. Patients were assigned to receive surgery only, surgery + i.p. chemotherapy or surgery (IPC) + i.p. chemotherapy + EIPL (EIPL-IPC). All patients received adjuvant chemotherapy with oral 5-FU derivatives. The 5-year overall survival rate was significantly better in the EIPL-IPC group (43.8%) compared with the IPC group (4.6%) ($p < 0.0001$) and the surgery only group (0%) ($p < 0.0001$). Uni- and multivariate analyses revealed EIPL to be the most significant prognostic factor.

This led to the investigation of EIPL alone in an ongoing Japanese trial in patients with ≥ T3 carcinoma of the stomach [44]. Hereby, lavage of the peritoneal cavity after standard D2 gastrec-

tomy is either performed with < 3 l of saline or a total of 10 l of saline before closure of the abdomen with disease-free survival as the primary endpoint.

Intraperitoneal Immunotherapy

In a recent phase I/II study, the trifunctional antibody catumaxomab (anti-EpCAM × anti-CD3) was investigated in patients with epithelial cell adhesion molecule (EpCAM)-positive peritoneal carcinomatosis from gastric, colorectal, or pancreatic cancer [45]. EpCAM is overexpressed in tumor cells of more than 90% of patients with gastrointestinal (GI) cancer [46]. Although it is also expressed on normal epithelial tissues, it is specific for tumor cells in the peritoneal cavity because peritoneal cells are of mesothelial origin and therefore do not express EpCAM. Hereby, the trifunctional antibody binds to EpCAM on tumor cells and CD3 on T-lymphocytes. Its intact F_c region, composed of two potent immunoglobulin isotypes, binds to type I and III F_c receptors on accessory cells including monocytes, macrophages, and dendritic cells inducing an effective tumor cell killing [47, 48]. Catumaxomab showed an acceptable safety profile and median overall survival from the time of diagnosis of peritoneal carcimtosis was 502 days [45]. Another randomized phase II/III study has been performed in patients with symptomatic malignant ascites due to EpCAM + carcinomas, including 258 patients among which 66 suffered from gastric cancer. Puncture-free survival was significantly longer in the group with catumaxomab compared with that in the control group. In addition, overall survival was significantly prolonged in gastric cancer patients in a prospectively planned analysis (71 vs. 44 days; $p = 0.0313$) [49]. Catumaxomab has also been investigated specifically in 55 gastric cancer patients after resection of the primary tumor in a Phase II study with no impact of the immunotherapy on postoperative complications. However, due to the short follow-up period and the low number of patients, the efficacy of the therapy could not be assessed. The results of a single-arm follow-up trial (IP-CAT-GC-03) investigating i.p. immunotherapy with catumaxomab after neoadjuvant chemotherapy and gastrectomy are still pending (http://www.fresenius.com/documents/GC02_231208-e.pdf). A presently recruiting French phase II trial (IIPOP study) is investigating i.p. catumaxomab treatment in gastric cancer patients with limited PC (PCI ≤ 12) and complete surgical cytoreduction [50]. Patients are randomized to either receive a regimen with a cumulative dose of 100 µg or 140 µg catumaxomab. The primary endpoint of the trial is the 2-year overall survival.

Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

The beneficial effect of HIPEC in the treatment of PC from gastric cancer has been recently demonstrated by Yang et al. in a phase III trial [51]. Patients were randomized to either receive complete cytoreductive surgery alone ($n = 34$) or complete cytoreductive surgery followed by HIPEC ($n = 34$) consisting of 120-mg cisplatin and 30-mg mitomycin C in 6000 ml of normal saline at 43 °C over 60–90 min. Median survival was significantly increased in the group who received HIPEC, but was only 11 months (95% CI 10-11.9 months) compared to 6.5 months (95% CI 4.8–8.2 months) ($p = 0.046$).

The so-called GYMSSA trial (NCT00941655) investigated on the safety and efficacy of gastrectomy, metastasectomy plus systemic therapy (FOLFOXIRI regimen) compared to systemic chemotherapy alone (FOLFOXIRI). This trial was designed as a single-center trial randomizing only 16 patients. The primary endpoint was overall survival [52]. So far, no results are published. A larger trial that was conducted by Japanese and Korean trialists (JPRN-UMIN000001012) was stopped after randomization of 164 patients due to recommendations of the independent safety and monitoring board. In this study, noncurative gastrectomy including D1-dissection in patients with a single noncurable factor (liver metastasis or peritoneal seeding or para-aortic lymph node metastasis) followed by chemotherapy was compared to systemic chemotherapy alone. The

preliminary interims analysis revealed worse survival for patients undergoing surgery. Taking into consideration the results of those studies, non-curative gastrectomy may not be recommended despite promising results from retrospective analyses.

A presently recruiting German trial investigates cytoreductive surgery in gastric cancer and junctional adenocarcinomas with or without HIPEC after preoperative chemotherapy (GASTRIPEC trial, NCT02148988). Another ongoing German trial (HIPEC-Stomach, NCT01683864) tries to define the benefit of HIPEC treatment in patients with free tumor cells in the pretherapeutic staging laparoscopy. Patients are randomized to receive neoadjuvant chemotherapy followed by gastrectomy ± HIPEC. The basically same issue is addressed by an ongoing French study (GASTRICHIP trial, NCT01882933) [53] and the so-called PERISCOPE trial from the Netherlands (EUCTR2013-000138-37-NL).

Reconstruction

Several reconstruction techniques were evaluated over the past decades. However, the type of reconstruction mainly depends on the mode of gastrectomy being performed and is influenced by the localization of gastric cancer. In Eastern Asia simple Billroth-I reconstructions are much more common compared to the Western hemisphere due to the higher frequency of distal gastrectomies in Asia.

Pouch Reconstruction

Pouch reconstruction after distal gastrectomy appears to be an appealing method to restore the GI function, improve QoL, and reduce dumping syndromes after total gastrectomy due to presumed reservoir function mimicking a physiologic situation. Several older trials investigated on this issue before. The results of the early trials were summarized in a meta-analysis by Gertler et al. [54]. Conclusively, there was no statistically significant difference between pouch and Roux-en-Y reconstructions related to morbidity and mortality. Further, operating time and hospital stay were not longer for pouch reconstructions. It was further revealed that dumping syndromes and heart burn were significantly lower in the pouch group at 12 months after surgery. Another positive aspect for the pouch reconstruction was that food intake and weight gain were improved. However, this effect was not statistically different. All those improvements appear to be responsible for improvements in QoL, but this effect was only detectable 2 years after curative gastric cancer surgery.

Several later trials mainly from Japan aimed to evaluate possible advantages of pouch reconstructions. However, the results were quite heterogeneous. Ikeguchi et al. demonstrated improved recovery of body weight in pouch-reconstructed patients after total gastrectomy after randomization of only 29 patients [55], whereas Iwahashi revealed no particular advantages of the pouch after prospectively enrolling 44 patients [56].

A more recent trial from Japan investigated on the optimal size of the pouch. Tsujimoto and colleagues randomized patients into either long-pouch or short-pouch reconstructions. The trial results revealed that a short-pouch reconstruction improved eating capacity per meal and weight gain after surgery [57].

The concept of proximal gastrectomy for early gastric cancer in the upper third of the stomach gave rise to some interesting trials originating from Japan and Korea in order to reduce the frequency of total gastrectomies. These trials compared either jejunal interposition to RY reconstruction or jejunal interposition to jejunal pouch interposition after proximal gastrectomy. The first trial from Korea revealed after randomization of 51 patients that jejunal interposition was technically safe regarding operating time, hospital stay, and postoperative complication rates while demonstrating statistically significant advantages regarding reduction of postgastrectomy symptoms and nutritional status for jejunal interposition [58]. Iwata et al. further revealed that if a jejunal pouch is inserted between the esophagus and the remnant stomach, food intake,

meal volume, and weight gain were considerably improved [59]. This result was confirmed in the most recent trial on this topic by Takagawa and colleagues after randomization of 38 patients [60].

Ishikawa et al. investigated on the Roux-en-Y reconstruction compared to conventional BI reconstruction after distal gastrectomy in 50 patients [61]. The authors found that gastric stasis occurred significantly longer in the Roux-en-Y group compared to the BI group, while long-term esophagitis did not differ between the two techniques. Duodenogastric reflux was improved significantly in the RY group. Nonetheless, there was a significant longer hospital stay for patients undergoing RY reconstruction. Therefore, the authors concluded that BI anastomosis should be considered the reconstruction of choice in patients undergoing distal gastrectomy.

A more recent trial by Takiguchi et al. randomized 332 patients to either RY or BI reconstruction [62]. The primary outcome measure was QoL. The authors revealed that QoL, as determined by the EORTC QLQ-C30 questionnaire, was comparable between the two reconstruction types after distal gastrectomy. However, reflux symptoms occurred more frequently in the BI group. The immediate postoperative hospital stay however was significantly shorter in BI reconstructed patients due to increased frequency of nausea, vomiting, and discontinued food intake in the RY group with comparable postoperative morbidity [62, 63]. The 1-year follow-up results demonstrated no advantages of RY reconstruction related to nutritional status and body weight [64].

So far there is only one trial prospectively comparing RY to BI and BII reconstructions. A randomized controlled study included 159 patients undergoing distal gastrectomy. The authors concluded that there was a significant reduction of bile reflux. Again, they found no differences in postoperative QoL-index and nutritional status. Interestingly, the authors declared that the laparoscopic approach resulted in significantly improved QoL in the immediate postoperative period regardless of the applied reconstruction route [65].

Conclusively, many trials tried to evaluate the optimal way of reconstructing the GI passage after gastrectomy for cancer. Whereas Western trials were able to reveal advantages for pouch reconstructions in potential long-term survivors, the results of the Eastern Asian trials did not demonstrate convincing data for pouch reconstructions after total gastrectomy. The widely applied BI reconstructions in Korea and Japan are not suitable for Western patients due to the more frequent localization in the upper part of the stomach. Therefore, no clear conclusions may be drawn on a global scale. However, Roux-en Y reconstruction may be considered a safe method for all patients undergoing total gastrectomy with acceptable postoperative outcomes. Potential long-term survivors may further benefit from pouch reconstructions. Further trials will have to evaluate the potential benefits of totally laparoscopic reconstructions.

Trials on Perioperative Management for Gastric Cancer

Not only optimizations of the surgical procedures but also modern treatment concepts after surgery are considered to be of utmost importance to reduce postoperative morbidity and mortality in gastric cancer patients. Several modern modalities including fast-track concepts are covered by recent trials, which are described in the following section.

The value of *drain placement* after gastric cancer surgery was investigated on in a Korean trial in 2001. Kim and colleagues randomized 170 patients receiving either drain or no drain stratified by the type of surgery (subtotal/total gastrectomy) [66]. The authors found that drain placement did not provide benefit for patients up to 30 days after surgery. Another trial from Chile in 2005 surprisingly even demonstrated that drain placement resulted in statistically significant higher postoperative morbidity and longer hospital stay after evaluating 60 randomly assigned patients [67]. Another topic of research within prospective trials was the application of *nasojejunal probes* after total gastrectomy. Doglietto

et al. randomized 237 patients into two groups receiving either NG-tube or no tube [68]. They found that esophagojejunostomy disruption rates did not differ between the two groups. Further, there were no differences for major postoperative complications, mortality, initiation of liquid diet, hospital stay, postoperative pain, and abdominal distension. The authors therefore concluded that placement of an NG-tube may not be recommended in elective gastric cancer surgery. A Chinese trial reported by Li et al. confirmed these results in 161 patients [69]. Postoperative stay was further significantly prolonged in patients receiving NG-tubes.

Perioperative antibiotic prophylaxis is believed to be beneficial to reduce surgical site infections (SSIs). This issue was investigated in three independent prospectively RCTs. Again, all these trials originate from Japan. A study by Mohri et al. randomized 501 patients into two groups either receiving single-dose or multiple-dose antibiotics [70]. The primary endpoint was SSI. The authors concluded that SSI could not be reduced by a multiple dose. This result was confirmed by Haga et al. after randomizing 325 patients and by Imamura in 355 patients [71, 72].

Supplementation of *immunonutrition* to gastric cancer patients was investigated in several trials. Omega-3 fatty acids (O3FA)-enriched nutrition is supposed to reduce postoperative complications by attenuation of inflammatory immune responses. The first trial was reported from UK. This RCT randomized 221 patients. The results showed that although the plasma concentrations of O3FA were significantly increased compared to the control groups, there were no differences regarding postoperative morbidity and mortality. Further, there was no increase in overall HLA-DR expression on monocytes or activated T-lymphocytes [73]. This result was confirmed by a Japanese trial randomizing 244 well-nourished patients undergoing elective gastric cancer surgery [74]. In contrast, a Chinese trial investigating application of arginine-supplemented nutrition in 73 malnourished patients found a significantly improved overall survival, progression-free survival, and increased numbers of CD4+ T-cells, NK-cells, IgM, and IgG levels on postoperative day 7 for those patients receiving the arginine-enhanced nutrition [75]. The most recent trial by an Italian group combined arginine and O3FA-enriched diet in their study. Marano et al. demonstrated a significantly reduced incidence of postoperative infectious complications, anastomotic leakage, and hospital stay [76]. Interestingly, the reduction of CD4+ T-cells was significantly decreased in the group receiving the enhanced diet. However, those effects did not translate into reduced mortality.

Another interesting trial investigated on the effects of postoperatively administered *ghrelin* in patients undergoing total gastrectomy for cancer. Ghrelin is believed to increase appetite and improve food intake after gastric resection. In a phase II study from Japan by Adachi et al., 21 patients received either placebo or ghrelin postoperatively. The authors found that short-term administration resulted in significantly lessened weight loss and significantly increased food intake [77].

Pain management after radical gastrectomy was prospectively assessed in a Chinese trial. The authors compared patient-controlled epidural to patient-controlled intravenous analgesia in 67 patients. It was concluded that the epidural administration route resulted in significantly reduced pain scores, shorter time to GI passage, and shorter hospital stay [78].

The role of *oxygen application* in order to reduce anastomotic leakage was investigated by Schietroma et al. This study enrolled 171 patients receiving either FiO2 of 30 % or 80 % at the induction of anesthesia until 6 h after surgery [79]. It was demonstrated that administration of high-concentration oxygen was able to significantly reduce anastomotic dehiscence rate by 49 %.

Incidence of gall stones is believed to be increased after gastrectomy due to dissection of the vagal branches. However, concomitant removal of the gallbladder is supposed to increase postoperative morbidity. The role of *additional routine cholecystectomy* was investigated by the so-called CHOLEGAS trial from Italy. In the preliminary evaluation, the authors concluded

that concomitant cholecystectomy did not add additional perioperative morbidity and treatment cost [80].

The recent developments in perioperative care led to the development of *fast-track surgery* concepts. This kind of postsurgical care has been evaluated, and has demonstrated clinical safety not only in colorectal surgery but also in vascular and orthopedic surgery before. Therefore, fast-track surgical treatment concepts were also evaluated for gastric cancer surgery. The fast track incorporated results from earlier trials such as renunciation of drain placement and naso-jejunal tubes, use of epidural analgesia, early mobilization and enteral nutrition, and modern anesthestic fluid management. A Chinese trial demonstrated shorter hospital stay, less fever, earlier bowel movement, less medical cost, and, most important, higher QoL scores at the hospital discharge. Further, inflammatory reactions represented by IL-6, TNF-alpha, and CRP (C-reactive protein) were significantly lower in the fast-track group compared with the conventional care group [81]. However, the surgical approach in that trial was essentially different: the fast-track group received laparoscopic surgery and the conventional group underwent open surgery. This might be an essential point of debate, as it is well known that surgical trauma is reduced by laparoscopic surgery. Another trial by Chen et al. more or less confirmed those results after randomization of 88 patients [82]. A Korean trial omitted the possible bias by comparing open to laparoscopic surgery in 47 patients. Again, the fast-track group had shorter hospital stay, but there were no differences in time to bowel movement and pain intensity. Most importantly, fast-track patients revealed improved postsurgical QoL as evaluated by the EORTC-QoL questionnaire [83]. The most recent trial by Feng et al. revealed the benefits in gastric cancer patients undergoing radical open surgery: time to bowel movement was shorter, postoperative pain was less, postoperative stay was shorter, and the cost of hospitalization was significantly reduced in the fast-track group [84].

Conclusively, the trials on perioperative treatment concepts may be considered as substantial improvements in modern gastric cancer surgery. Conventional concepts, such as drain placements and conservative managements, have been overcome. Fast-track treatment can be considered safe and feasible. So far, it remains elusive if those treatments may also translate into improved oncologic outcomes.

Cardia Cancer

Surgical treatment of proximal gastric cancer, which is mainly found in the Western hemisphere, remains a significant challenge for surgeons. One of the main issues was the question if cancer at the gastroesophageal junction should be treated either by transabdominal or transthoracic approaches. A Japanese trial investigating on 167 patients demonstrated that the transthoracic approach did not reveal any substantial advantages compared with the transabdominal surgery [85]. In addition, the trial revealed increased morbidity in the transthoracic group. This finding was reproduced by a Dutch trial after randomization of 220 patients [86]. However, in the subgroup analysis, the transthoracic approach provided some benefits for Siewert type I gastroesophageal junction cancers.

Final Conclusions

In conclusion, there is a variety of trials investigating on outcome improvements of gastric cancer. The International Clinical Trials Registry Platform by the WHO momentarily lists 561 actively recruiting trials but only 74 trials in which surgery is part of the intervention (Table 20.1). However, most of those trials are evaluating new chemotherapeutic regimens and drugs for gastric cancer management. Surgical trials must be in the center of interest, because surgery for gastric cancer is the only curative treatment option momentarily. The different outcomes of the trials investigating on perioperative chemotherapy demonstrated the importance of surgical quality control. Similarly to the KLASS and SENORITA

Table 20.1 Currently recruiting surgical trials in gastric cancer

Trial ID	Title	Primary sponsor	Registration	Web link
NCT01065688	A trial of reconstruction after distal gastrectomy for gastric cancer	Wakayama Medical University	08/02/2010	http://clinicaltrials.gov/show/NCT01065688
NCT01375738	Improving diabetes by reconstruction methods in gastric cancer patients with diabetes mellitus	Yonsei University	27/05/2011	http://clinicaltrials.gov/show/NCT01375738
NCT01456598	Efficacy of laparoscopic subtotal gastrectomy with D2 lymph node dissection for locally advanced gastric cancer	Ajou University School of Medicine	11/10/2011	http://clinicaltrials.gov/show/NCT01456598
NCT01528059	Roux-en-Y versus Billroth II reconstruction after subtotal gastrectomy in gastric cancer comorbid with type II diabetes	Feng Zheng	02/02/2012	http://clinicaltrials.gov/show/NCT01528059
NCT01742806	Clinical study for the impact of bio-absorbable felt (NEOVEIL®) with fibrin sealant on removal of drainage tube after minimally invasive gastrectomy for gastric cancer	Yonsei University	20/11/2012	http://clinicaltrials.gov/show/NCT01742806
NCT01838109	Postoperative oral nutritional supplementation after major gastrointestinal surgery	Seoul National University Hospital	10/04/2013	http://clinicaltrials.gov/show/NCT01838109
NCT00757640	Gastrectomy plus prophylactic cholecystectomy in gastric cancer surgery	Italian Research Group for Gastric Cancer	20/09/2008	http://clinicaltrials.gov/show/NCT00757640
NCT00677456	Evaluation of four reconstructions after total gastrectomy	Tang-Du Hospital	12/05/2008	http://clinicaltrials.gov/show/NCT00677456
NCT00992199	Randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable local advanced gastric cancer	Fudan University	08/10/2009	http://clinicaltrials.gov/show/NCT00992199
NCT00164918	Role of routine nasogastric decompression after subtotal gastrectomy	Chinese University of Hong Kong	12/09/2005	http://clinicaltrials.gov/show/NCT00164918
NCT00452751	Comparison of laparoscopic versus open gastrectomy for gastric cancer: a prospective randomized trial	National Cancer Center, Korea	26/03/2007	http://clinicaltrials.gov/show/NCT00452751
NCT01836991	D2 and D2+ radical surgery for the treatment of advanced distal gastric cancer	Zhejiang Cancer Hospital	17/04/2013	http://clinicaltrials.gov/show/NCT01836991
NCT00741676	Comparison of the laparoscopy-assisted distal gastrectomy and open distal gastrectomy for advanced gastric cancer	The Catholic University of Korea	25/08/2008	http://clinicaltrials.gov/show/NCT00741676
NCT01179750	The use of ultrasonic coagulating shears compared to monopolar electrocautery in open gastric cancer surgery	Samsung Medical Center	27/07/2010	http://clinicaltrials.gov/show/NCT01179750
NCT01804998	Multicenter phase III trial of laparoscopic sentinel node biopsy	National Cancer Center, Korea	04/03/2013	http://clinicaltrials.gov/show/NCT01804998
NCT01657175	Quality of life after oesophageal or gastric cancer surgery	Region Skane	29/06/2012	http://clinicaltrials.gov/show/NCT01657175

Table 20.1 (continued)

Trial ID	Title	Primary sponsor	Registration	Web link
NCT01257711	A study comparing Billroth II with Roux-en-Y reconstruction for gastric cancer	National Healthcare Group, Singapore	08/06/2010	http://clinicaltrials.gov/show/NCT01257711
NCT02164448	The effects of intraoperative dexmedetomidine infusion on postoperative bowel movement in patients undergoing laparoscopic gastrectomy	Yonsei University	09/06/2014	http://clinicaltrials.gov/show/NCT02164448
NCT01996059	Functional jejunal interposition improve nutritional status after total gastrectomy	Sun Yat-sen University	19/11/2013	http://clinicaltrials.gov/show/NCT01996059
NCT01433861	Laparoscopy-assisted proximal gastrectomy versus and laparoscopy-assisted total gastrectomy	Seoul National University Bundang Hospital	10/09/2011	http://clinicaltrials.gov/show/NCT01433861
NCT02064803	Gastric partitioning procedure for the treatment of unresectable and obstructive distal gastric cancer	Instituto do Cancer do Estado de São Paulo	31/01/2014	http://clinicaltrials.gov/show/NCT02064803
NCT02123407	Clinical study on the harvesting lymph nodes with carbon nanoparticles for advanced gastric cancer	Peking University	21/04/2014	http://clinicaltrials.gov/show/NCT02123407
NCT02158988	Cytoreductive surgery (CRS) with/without HIPEC in gastric cancer with peritoneal carcinomatosis	Charite University, Berlin, Germany	04/05/2014	http://clinicaltrials.gov/show/NCT02158988
NCT02140034	Extensive peritoneal lavage after curative gastrectomy for gastric cancer: a randomised controlled trial	National University Hospital, Singapore	14/05/2014	http://clinicaltrials.gov/show/NCT02140034
NCT02120885	An effect of an individualized physical activity intervention for gastric cancer patient undergoing minimally invasive gastrectomy: a phase III, prospective randomized controlled trial	Yonsei University	31/03/2014	http://clinicaltrials.gov/show/NCT02120885
NCT02168426	Randomized control trial on seprafilm and guardix in preventing ileus	Gachon University Gil Medical Center	18/06/2014	http://clinicaltrials.gov/show/NCT02168426
NCT01704664	Prospective study of the effect of perioperative immunonutrition on the immune host defense and the phagocytic and bactericidal activity of blood platelets in gastric cancer patients	Medical University of Bialystok	26/09/2012	http://clinicaltrials.gov/show/NCT01704664
EUCTR2011-004405-25-DE	Study for prevention of peritoneal carcinomatosis in patients with stomach cancer—HIPEC_Stomach	University Hospital Tübingen	06/01/2012	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-004405-25
EUCTR2005-004280-31-GB	Hyperthermic intraperitoneal chemotherapy—gastric cancer—HIPEC in gastric cancer	University of Dundee	22/09/2005	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-004280-31

Table 20.1 (continued)

Trial ID	Title	Primary sponsor	Registration	Web link
EUCTR2006-006088-22-DE	Prospective multicenter phase III clinical trial using cytoreductive surgery with hyperthermic intraoperative chemotherapy (HIPEC) after preoperative chemotherapy in patients with peritoneal carcinomatosis of gastric cancer incl. adenocarcinoma of the esophagogastreal junction	Charité—Universitätsmedizin Berlin	14/02/2011	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-006088-22
NCT01471132	Sequential HIPEC of oxaliplatin and paclitaxel for gastric cancer patients with peritoneum metastasis	Peking University	01/11/2011	http://clinicaltrials.gov/show/NCT01471132
NCT01544413	Quality control study of laparoscopic sentinel node biopsy in early gastric cancer	National Cancer Center, Korea	16/02/2012	http://clinicaltrials.gov/show/NCT01544413
NCT01642953	Early recovery after gastric cancer surgery	Ajou University School of Medicine	14/07/2012	http://clinicaltrials.gov/show/NCT01642953
NCT01926743	Identification of complete lymph node removal by application of near infrared fluorescence imaging in laparoscopic and robotic gastrectomy	Yonsei University	18/08/2013	http://clinicaltrials.gov/show/NCT01926743
NCT01584336	Laparoscopy-assisted total gastrectomy for clinical stage-I gastric cancer (KLASS-03)	Soonchunhyang University Hospital	22/04/2012	http://clinicaltrials.gov/show/NCT01584336
NCT01283893	Standardization of D2 lymphadenectomy and surgical quality control: KLASS-02-QC	Yonsei University	24/01/2011	http://clinicaltrials.gov/show/NCT01283893
NCT01319084	Development of a versatile intra-operative on-screen audiovisual mentoring system using Tilepro^{TM} Program for robotic gastrectomy	Yonsei University	18/03/2011	http://clinicaltrials.gov/show/NCT01319084
NCT01643811	Effect of gastrectomy and anastomosis on diabetes and hypertension in early gastric cancer patients	National Cancer Center, Korea	11/07/2012	http://clinicaltrials.gov/show/NCT01643811
NCT01919242	Postoperative morbidity and mortality after gastrectomy for gastric cancer: prospective cohort study	Yonsei University	07/08/2013	http://clinicaltrials.gov/show/NCT01919242
NCT01714622	Prospective cohort study for analyzing the effect of gastric cancer surgery to the metabolic syndrome and insulin resistance	Yonsei University	17/10/2012	http://clinicaltrials.gov/show/NCT01714622
CTRI/2013/08/003882	Comparison of D2 versus D3 surgical procedure outcome in locally advanced gastric cancer patients following perioperative chemotherapy	Tata Memorial Hospital	06-08-2013	http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=6992
JPRN-UMIN000000596	A randomised phase II trial of preoperative exercise to reduce operative risk in gastric cancer patients with metabolic syndrome	AEGES Study Group	07/02/2007	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000001544	Multicenter prospective randomized trial about clinical effect of absorbable suture materials against surgical site infection in digestive surgery	Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University	01/01/2009	http://www.umin.ac.jp/ctr/index.htm

Table 20.1 (continued)

Trial ID	Title	Primary sponsor	Registration	Web link
JPRN-UMIN000002938	Effects of perioperative and long-term nutritional management in elderly patients undergoing surgery for gastric cancer	Department of Surgical Oncology, Kanazawa Medical University	25/12/2009	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000003364	Effects of preservation of celiac branch of the vagus nerve after distal gastrectomy for gastric cancer. A prospective randomized controlled phase II study	Osaka University, Graduate School of Medicine, Gastroenterological Surgery	23/03/2010	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000003420	Randomized controlled trial to evaluate laparoscopic versus open surgery for advanced gastric cancer (JLSSG0901: Adv.GC-LAP/OPEN, PII/III)	Japanese Laparoscopic Surgery Study Group (JLSSG)	31/03/2010	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000003688	A phase III trial to evaluate bursectomy for patients with SS/SE gastric cancer (JCOG1001, BURSECTOMY PHASE III)	Japan Clinical Oncology Group (JCOG)	01/06/2010	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000005421	Randomized phase II study of omentum-preserving gastrectomy for advanced gastric cancer	Kanagawa Prefectural Ashigarakami Hospital	11/04/2011	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000005907	A phase III trial to evaluate extensive intraoperative peritoneal lavage for patients with SS/SE/SI gastric cancer (CCOG 1102, extensive lavage phase III)	Chubu Clinical Oncology Group (CCOG)	08/07/2011	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000006380	Phase III trial to evaluate EPA-enriched immunonutrition by perioperative prosure in total gastrectomy for T2-T4a gastric cancer	Non-profit organization KSATTS	21/09/2011	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000007457	Clinical evaluation of transversus abdominis plane block and celecoxib after laparoscopic gastrectomy	Kansai Medical University	01/04/2012	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000007755	Efficacy of free access, slender port for reduced port surgery: a prospective study	Digestive Disease Center, Showa University Northern Yokohama Hospital	13/04/2012	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000008056	Randomised phase II trial of efficacy of early nutritional intervention with an elemental diet (ELENTAL) for gastric cancer patients after surgical treatment	KSES	30/05/2012	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000009163	Randomized phase III trial of benefit of additional cholecystectomy in total gastrectomy for gastric cancer patients	Second Department of Surgery Wakayama Medical University	25/10/2012	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000010568	Randomised clinical trial to evaluate postoperative quality of life and body weight loss with the use of EPA-enriched nutrient for resectable gastric cancer patients	Jichi Medical University Hospital	23/04/2013	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000013768	Phase III study for efficacy of V-Loc 180 for laparoscopic distal gastrectomy	Osaka Medical College	21/04/2014	http://www.umin.ac.jp/ctr/index.htm

Table 20.1 (continued)

Trial ID	Title	Primary sponsor	Registration	Web link
ChiCTR-TRC-13004004	Long-term quality of life and prognosis comparison between antrum-preserving double tract reconstruction of jejunal interposition procedure and traditional digestive reconstruction in proximal gastrectomy for adenocarcinoma of the esophagogastric junction: a prospective randomized controlled trial	Affiliated Hospital of North Sichuan Medical College	2013-12-19	http://www.chictr.org/en/proj/show.aspx?proj=5774
ChiCTR-TRC-13003632	The postoperative outcome of gastric cancer: bursectomy VS no bursectomy	Xijing Hospital, Fourth Military Medical University	2013-09-27	http://www.chictr.org/en/proj/show.aspx?proj=5672
ChiCTR-TRC-13003619	The outcome of patients receiving total gastrectomy: early oral feeding versus delayed oral feeding	Xijing Hospital, Fourth Military Medical University	2013-09-23	http://www.chictr.org/en/proj/show.aspx?proj=5644
ChiCTR-TRC-13003615	The outcome of patients receiving distal gastrectomy: gastric decompression versus no gastric decompression	Xijing Hospital, Fourth Military Medical University	2013-09-22	http://www.chictr.org/en/proj/show.aspx?proj=5640
ChiCTR-TRC-13003614	The outcome of patients receiving laparoscopic distal gastrectomy: gastric decompression versus no gastric decompression	Xijing Hospital, Fourth Military Medical University	2013-09-22	http://www.chictr.org/en/proj/show.aspx?proj=5641
ChiCTR-TRC-13003613	The outcome of patients receiving laparoscopic distal gastrectomy: early oral feeding versus delayed oral feeding	Xijing Hospital, Fourth Military Medical University	2013-09-22	http://www.chictr.org/en/proj/show.aspx?proj=5646
ChiCTR-TRC-10001611	Fast-track surgery (FTS) improves postoperative recovery in patients with gastric cancer: a randomized comparison with conventional postoperative care	Affiliated Hospital of Qingdao University Medical College	2011-10-10	http://www.chictr.org/en/proj/show.aspx?proj=1685
ChiCTR-TRC-10001517	Study of preoperative oral carbohydrate-rich solution ameliorating insulin resistance in postoperative patients of radical gastrectomy	Affiliated Hospital of Qingdao University Medical College	2011-09-16	http://www.chictr.org/en/proj/show.aspx?proj=1435
ChiCTR-TRC-11001440	The randomized controlled study of perioperative rapid rehabilitation strategies, and traditional methods for gastric cancer patients with early postoperative rehabilitation	Xijing Hospital of Digestive Diseases; the Fourth Military Medical University	2011-07-29	http://www.chictr.org/en/proj/show.aspx?proj=1481
ChiCTR-TRC-10001434	Long-term quality of life comparison of Billroth-I versus Roux-en-Y reconstruction in radically distal gastrectomy for gastric cancer: a prospective randomized controlled trial	West China Hospital, Sichuan University, China	2011-07-27	http://www.chictr.org/en/proj/show.aspx?proj=1417
CTRI/2009/091/000071	A clinical trial to study the effects of two forms of reconstruction, uncut Roux-en-Y gastrojejunostomy and standard Roux-en-Y gastrojejunostomy following partial gastrectomy or palliative bypass in patients with cancer of stomach	Christian Medical College, Vellore, India	02-04-2009	http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=343
JPRN-UMIN000000476	Multi-center clinical trial for diagnostic value of sentinel node biopsy to detect lymph node metastasis in gastric cancer	Japanese Society for Sentinel Node Navigation Surgery	01/09/2006	http://www.umin.ac.jp/ctr/index.htm

Table 20.1 (continued)

Trial ID	Title	Primary sponsor	Registration	Web link
JPRN-UMIN000001787	Limited surgery for early gastric cancer using sentinel node navigation	Department of Surgery, National Defense Medical College	19/03/2009	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000002386	Evaluation of sentinel lymph nodes in digestive tract using mini-gamma camera	Chiba University	26/08/2009	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000003339	Prospective cohort study of procedures for early gastric cancer in the upper third of the stomach	Multicenter Clinical Study Group of Osaka	16/03/2010	http://www.umin.ac.jp/ctr/index.htm
JPRN-UMIN000008624	Methylene blue-assisted lymph node dissection in gastric cancer specimens	Department of Gastrointestinal Surgery, Kanagawa Cancer Center	05/08/2012	http://www.umin.ac.jp/ctr/index.htm
NCT01725789	Ferinject® assessment in gastrectomy patients with acute isovolemic anemia (FAIRY)—a randomized patient-blind controlled phase III study to compare the efficacy and safety of intravenous ferric carboxymaltose (Ferinject®) with placebo in patients with acute isovolemic anemia after gastrectomy	National Cancer Center, Korea	03/11/2012	http://clinicaltrials.gov/show/NCT01725789
EUCTR2013-000138-37-NL	Treatment of peritoneal dissemination in stomach cancer patients with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy	NKI-AvL	01/07/2013	https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000138-37

trials, investigators should actively consider implementation of quality control studies before launching phase III investigations. Only standardized and adequate surgical resection may extinguish doubts on the value of perioperative interventions. Further, it has to be noted that most of the surgical trials and innovations originate from East Asia, namely from Korea and Japan. China will be playing a major role in the conduct of modern surgical trials in the near future. Therefore, it remains elusive if the results of those trials may be transferable to Western patients. Western investigators should start to initiate multinational cooperation in order to confirm or reject results created by the East Asian trials due to the dramatically reduced incidence of gastric cancer in the Western hemisphere.

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Part IV

Neoadjuvant and Adjuvant Treatments for Gastric Cancer and Targeted Therapy

21 Neoadjuvant and Adjuvant Treatment—Strategies and Clinical Trials—Western Perspective

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Introduction

Gastric cancer, an uncommon but highly virulent malignancy in the USA, was diagnosed in 22,220 patients in 2014, with 10,990 deaths [1]. In comparison to its relative rarity in the USA, gastric cancer is endemic in parts of East Asia, which account for more than half of the approximately 1 million cases that develop per year globally [2]. Despite the much higher incidence, East Asian patients with gastric cancer do appear to have better prognosis [3].

In the USA, the incidence of gastric cancer has decreased significantly in the past 50 years but the location of the primary tumor has also changed. Distal gastric cancer, which previously predominated, has become uncommon, while the incidence of tumors of the gastric cardia and gastroesophageal junction (GEJ) have increased 4–10 % per year among US men since 1976 [4, 5].

Changing epidemiologic factors account for the increasing incidence of proximal tumors. Chronic infection with *Helicobacter pylori* has been implicated in the development of gastric cancer on the basis of epidemiological evidence [6]. A decline in *H. pylori* infection in the USA has led to an overall decrease in the number of gastric cancer cases. On the other hand, proximal and GEJ tumors are now more common because of an increased incidence of gastroesophageal reflux disease [7] and obesity [8].

For locally advanced gastric cancer, surgery remains the most important component of curative therapy. Numerous studies have evaluated pre- and postoperative strategies for locally advanced disease, including chemotherapy or chemoradiation. As a whole, these studies show that some treatment in addition to surgery clearly improves outcomes. As an important clarification and consistent with guidelines from the National Comprehensive Cancer Network, our practice pattern is to apply the conclusions of these studies only to Siewert Type III GE junction and gastric adenocarcinomas [9]. Siewert Type I tumors arise from the distal esophagus and infiltrate the GEJ from above while Type III tumors are gastric cardia tumors that infiltrate the GEJ from below; Type II tumors are true tumors of the GEJ. Preoperative chemoradiation is a validated option for lower esophageal and Siewert Type I/II GEJ adenocarcinomas [10] but this approach and these diseases are not the focus of this review.

Outcomes in Asia

Before discussing studies that have been performed in the West, it is important to highlight that survival rates with surgery alone in East Asia (60–70 %) exceed those in the USA (40 % in the Intergroup 116 study described below [11]) and

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even in European studies where curative extended lymph node D2 resections were performed (47% 5-year OS) [12]. Our group previously compared the single-institution experience at Memorial Sloan Kettering with that of a single Korean hospital (Seoul St. Mary's Hospital) [13]. The Korean patients were younger, more likely to have distal tumors (while their US counterparts were more likely to have proximal tumors) and had earlier stage tumors with more lymph nodes harvested at surgery. Despite controlling for these and other known prognostic factors, the Korean patients consistently had a higher disease-specific survival (hazard ratio or HR 1.3; 95% confidence interval or CI 1.0–1.6, $p=0.008$). This improved survival may suggest that there are differences in the underlying biology of East Asian gastric cancers that convey a better prognosis. As such, a comparison of outcomes in studies performed in East Asia must be done with some degree of caution.

Preoperative Chemotherapy

A strategy of perioperative chemotherapy is the predominant approach in Europe and increasingly in the USA, based primarily on the phase III Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial performed in the UK [14]. This trial randomized 503 patients with gastric cancer to three cycles each of pre- and postoperative epirubicin/cisplatin/5-fluorouracil or 5-FU (ECF) and surgery or surgery alone. Perioperative chemotherapy resulted in significant improvement in 5-year OS (36 vs. 23%, $p=0.009$), establishing this regimen as a standard of care.

A similar degree of benefit was also noted in the contemporaneous French FFCD 9703 trial of 224 patients with esophagogastric adenocarcinoma [15]. Patients were randomized to six cycles of perioperative 5-FU/cisplatin followed by surgery versus surgery alone. Perioperative chemotherapy on this trial was associated with a significant improvement in 5-year disease-free survival (DFS; 34 vs. 19%, $p=0.003$) and OS (38 vs. 24%, $p=0.02$). Although comparisons between different clinical trials must be made cautiously, the survival benefit seen with 5-FU/cisplatin on this trial appears to be nearly identical to that seen with ECF in the MAGIC trial. As such, a 5-FU/platinum doublet is also an option in the perioperative setting, especially for patients who are not candidates for or have poor tolerance of the addition of an anthyracycline.

On the other hand and most recently, the European EORTC 40954 trial evaluated a strategy of preoperative 5-FU/leucovorin/cisplatin in 144 patients with GEJ and gastric adenocarcinoma [16]. The trial was stopped because of poor accrual, which limits the power of the study, and no differences in survival were detected. These data are summarized in Table 21.1.

Table 21.1 Results of phase III pre- or perioperative chemotherapy trials in gastric and GE junction cancer

Treatment	No. of patients	R0 resection rate (%)	Pathologic CR rate	Survival		Local failure*	Reference
				Median	Overall		
Periop ECF + surgery	250	69	0%	*24 months*	5-year *36%*	14%	Cunningham et al. [14]
Surgery	253	66	N/A	*20 months*	5-year *23%*	21%	
Periop 5FU/Cis + surgery	109	*87*	NS	NS	5-year *38%*	24%	Ychou et al. [15]
Surgery	110	*74*	N/A	NS	5-year *24%*	26%	
Preop 5FU/LV/Cis + surgery	72	*82*	7.1%	64.6 months	2-year 73%	NS	Schumacher et al. [16]
Surgery	72	67	N/A	52.5 months	2-year 70%		

Cis cisplatin, *CR* complete response, *ECF* epirubicin, cisplatin, 5-fluoruoracil, *LV* leucovorin, *N/A* not applicable, *NS* not stated

Postoperative Chemoradiation

In the USA, a standard of care is postoperative chemoradiation for resected GEJ and gastric cancers based primarily on the results of the Intergroup 116 trial [11]. This trial randomized 556 patients to adjuvant chemotherapy and chemoradiation with bolus 5-FU/leucovorin versus observation alone following surgery. Patients who received adjuvant chemoradiation had an improvement in 3-year OS (51 vs. 40%, $p=0.005$).

Despite this positive result, this trial is frequently criticized because of the relatively suboptimal surgical resections that were performed—54% of patients had less than a D1 or D2 resection, which is less than a complete dissection of the involved lymph nodes. It has been argued that radiation in this setting compensated for inadequate surgery because the greatest impact of adjuvant chemoradiation was a reduction in local recurrence of cancer. This is underscored by the observation that the major impact of postoperative chemoradiotherapy is to reduce local tumor recurrence. Such benefits may not be seen for radiotherapy if a more complete D1 or D2 surgical resection is undertaken.

Based on the results of the Intergroup trial, the Cancer and Leukemia Group B launched and completed the 80101 trial, a trial attempting to intensify the chemotherapy delivered as postoperative therapy. Five hundred and forty six gastric cancer patients were enrolled. The standard arm consisted of systemic bolus 5-FU/leucovorin preceding and following chemoradiation with infusional 5-FU while the experimental arm changed the systemic chemotherapy by replacing the bolus 5-FU/leucovorin with the ECF regimen. Results have been presented in abstract form and reveal no improvement in 3-year DFS (47 vs. 46%) or OS (52 vs. 50%) with the addition of an anthracycline and platinum compound to 5-FU [17]. These results are also virtually identical to the outcomes in the adjuvant chemoradiation arm of the Intergroup 116 trial. These results indicate that 5-FU monotherapy, combined with radiation, remains a standard of care, in particular in patients who have undergone less than a D1 or D2 resection. Adding cisplatin and epirubicin to adjuvant chemotherapy failed to improve survival. ECF should not be used as an adjuvant chemotherapy regimen, although pre- and postoperative ECF without radiation therapy remains a care standard. These results are summarized in Table 21.2.

Radiation After D2 Gastrectomy

An attempt to answer the question of whether there is a benefit for postoperative radiation in patients who have undergone a D2 gastrectomy was made by investigators of the Korean

Table 21.2 Results of phase III postoperative chemoradiation trials in gastric and GE junction cancer

Treatment	No. of patients	Disease-free survival		Overall survival		Local failure[a]	Reference
		Median	Overall	Median	Overall		
Surgery	275	*19 months*	3-year *31%*	*27 months*	3-year *41%*	29%	MacDonald et al. [11]
Postop 5FU/LV → 5FU/RT → 5FU/LV	281	*30 months*	3-year *48%*	*36 months*	3-year *50%*	19%	
Postop 5FU/LV → 5FU/RT → 5FU/LV	280	30 months	3-year 46%	36.6 months	3-year 50% 5-year 41%	NS	Fuchs et al. [17]
Postop ECF → 5FU/RT → ECF	266	28 months	3-year 47%	37.8 months	3-year 52% 5-year 44%	NS	
Cape/cis	228	NS	3-year 74%	NS		8.3%	Lee et al. [18]
Cape/cis → chemoRT → cape/cis	230		3-year 78%			4.8%	

Cape capecitabine, *cis* cisplatin, *ECF* epirubicin/cisplatin/infusional 5-fluorouracil, *LV* leucovorin, *NS* not stated, *RT* radiotherapy

[a]Local failure with or without distant recurrence; numbers in *italics* indicate statistically significant differences

Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial. This study randomized 458 patients with stage IB-IV gastric cancer who had undergone D2 resections to either six cycles of adjuvant chemotherapy with the oral 5-FU pro-drug capecitabine and cisplatin or to two cycles of capecitabine/cisplatin before and after chemoradiation with capecitabine (Table 21.2; [18]). This study must of course be interpreted cautiously in a Western context but it does potentially offer insight into the benefit of radiation under these circumstances.

In the overall population, patients in the chemoradiation arm had a nonstatistically significant trend toward improved 3-year DFS (78.2 vs. 74.2%, $p=0.09$). In a subgroup analysis of 396 patients with lymph node-positive disease, there was a statistically significant improvement in 3-year DFS in the chemoradiation arm (77.5 vs. 72.3%, $p=0.04$). There was no difference in the rate of locoregional or metastatic recurrence in either arm. Based on these results, a follow-up study (ARTIST-II, NCT01761461) is ongoing for patients with lymph node-positive disease; in addition to being randomized to receive chemoradiation or chemotherapy alone, the systemic chemotherapy will consist of another 5-FU pro-drug S-1 alone or with the platinum compound, oxaliplatin.

Unfortunately, the results of the ARTIST trial do not provide definitive evidence for incorporating radiation into adjuvant therapy for optimally resected patients, although there may be a small absolute benefit of about 5% in 3-year DFS for radiation. The finding that radiation appears to benefit patients with lymph node-positive disease is somewhat counterintuitive since these patients are presumed to be at greater risk for developing distant metastases than patients with lymph node-negative disease and might therefore be expected to derive less benefit from an approach designed to improve locoregional control. Finally, even if one were to adopt a strategy of adjuvant chemoradiation for this population, it is entirely unclear that the systemic chemotherapy should consist of a fluoropyrimidine/platinum doublet since the negative CALGB 80101 study has already shown no benefit to adding cisplatin (and an anthracycline) to a fluoropyrimidine.

In addition to the ARTIST-II study, the Dutch CRITICS study (NCT00407186) and the Australian TOPGEAR trial (NCT01924819) are also trying to definitively address the benefit of adding chemoradiation to post- and preoperative chemotherapy, respectively.

Postoperative Chemotherapy

In the modern era, there are no large US or European studies that have evaluated a purely adjuvant chemotherapy approach following surgery. However, older studies did investigate this approach. An individual patient data meta-analysis was performed on 3838 patients enrolled in 17 randomized studies between 1974–2001; most of these studies enrolled < 200 patients and included studies performed in the USA, Europe, and Asia [19]. The meta-analysis revealed a statistically significant benefit in terms of OS (HR 0.82; 95% CI 0.76–0.90; $p<0.001$) and DFS (HR 0.82; 95% CI 0.75–0.90, $p<0.001$). This translated into a 6% absolute improvement in 5-year OS.

Partly because of the significantly superior outcomes with surgery alone, the standard of care in East Asia is for upfront surgery followed by adjuvant chemotherapy. To date, two trials in East Asia of resectable gastric cancer have found a benefit for adjuvant fluoropyrimidines as monotherapy or in combination with a platinum agent. Again, whether the results of these studies can be fully extrapolated to a Western population is not known. The results are summarized in Table 21.3.

The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) study was performed in Japan. In this study of 1059 patients with stage II/III gastric cancer who had undergone D2 resections, patients were randomized to 1 year of adjuvant S-1 versus observation [20]. Five-year outcomes for this trial were updated, confirming that adjuvant S-1 is associated with significant improvements in 5-year OS (71.7 vs. 61.1%, HR 0.67, 95% CI 0.54–0.83) compared to observation alone [21].

The second trial is the capecitabine and oxaliplatin adjuvant study in stomach cancer (CLASSIC) trial, which was performed in 1035 East Asian patients who had undergone a D2 resection

Table 21.3 Results of phase III postoperative chemotherapy trials in gastric cancer

Treatment	No. of patients	Survival		Local failure	Reference
		Median	Overall		
Surgery	530	NR	5-year *61%*	2.8%	Sakuramoto et al. [20]; Sasako et al. [21]
Surgery + S-1	529	NR	5-year *72%*	1.3%	
Surgery	515	NR	5-year *78%*	44%	Bang et al. [22]; Noh et al. [23]
Surgery + Capeox	520	NR	5-year *69%*	21%	
Adjuvant UFT or S-1	723	NS	3-year[a] 54%	NS	Tsuburaya et al. [24]
Adjuvant paclitaxel → UFT or S-1	710	NS	3-year[a] 57%	NS	

Capeox capecitabine/oxaliplatin, *CR* complete response, *N/A* not applicable, *NR* not reached, *UFT* tegafur/uracil
[a]Disease-free survival. Numbers in italics indicate statistically significant differences

of stage II-IIIB gastric cancer [22]. Patients were randomized to 6 months of adjuvant capecitabine/oxaliplatin versus observation. Updated survival data confirm improved 5-year OS for patients who received chemotherapy (78 vs. 69%, HR 0.66, $p=0.0015$); 5-year DFS was also improved (68 vs. 53%, HR 0.58, $p<0.0001$) [23].

On the other hand, a lack of benefit for adding a taxane to a fluoropyrimidine in the adjuvant setting was revealed by the results of the recently published SAMIT study conducted in Japan [24]. One thousand, four hundred and thirty-three evaluable patients with T4a or T4b tumors who had undergone initial surgery were randomized to receive either an oral fluoropyrimidine alone or paclitaxel preceding it. There was no improvement in 3-year DFS for the group that also received a taxane (57.2 vs. 54.0%, $p=0.273$), suggesting that more chemotherapy in an unselected population may not be a beneficial strategy.

Conclusion

Gastric cancer remains a significant worldwide health problem, with proximal gastric and GEJ tumors an emerging epidemic in Western countries.

In the past 15 years, phase III studies performed in the West have shown a clear benefit for additional therapy other than surgery. In the USA, the two validated strategies are perioperative chemotherapy (based on the MAGIC study) or postoperative chemoradiation (based on the Intergroup 116 study). Given the similar improvements in outcomes with both approaches (an approximate 10–15% improvement in OS), our preference is for perioperative chemotherapy.

This approach is based on the following assumptions: that patients who undergo upfront surgery are at risk for developing metastatic disease at an early interval; that gastric cancer is a moderately chemosensitive disease; that upfront chemotherapy might control micrometastatic disease; that the benefit of adjuvant radiation remains unclear in our patient population, where D2 lymph node dissections are standard and; that adjuvant chemotherapy following partial or total gastrectomy is potentially associated with poorer therapy tolerance and potentially a lesser ability to deliver all planned adjuvant therapy.

In comparison, the standard of care in East Asia is for upfront surgery and adjuvant chemotherapy, where 1 year of an oral fluoropyrimidine or 6 months of a fluoropyrimidine/platinum doublet result in the same 10–15% improvement over surgery alone. Given that the magnitude of the absolute benefit is nearly the same with all of these approaches on the basis of comparing across phase III studies, it would be relatively unlikely that either a perioperative or a postoperative approach would emerge as the clearly superior strategy.

Therefore, what may be more critical than the timing of chemotherapy is that patients at a minimum receive a fluoropyrimidine/platinum in the perioperative setting or a fluoropyrimidine in the adjuvant setting (based on the results of the studies above). Whether the addition of a platinum compound to a fluoropyrimidine in the postoperative setting or of radiation to either pre- or postoperative chemotherapy will further

improve outcome will hopefully be elucidated in the next several years.

In addition, ongoing and planned studies, e.g., the MAGIC-B study which randomizes patients with resectable GEJ and gastric adenocarcinomas to perioperative chemotherapy with or without bevacizumab, an antibody against vascular endothelial growth factor, are incorporating robust correlative components, which may identify biomarkers that are prognostic or predictive of benefit from chemotherapy and/or targeted agents.

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22 Adjuvant and Neoadjuvant Treatment: Standard Treatment and Clinical Trials in the East

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Actual Standard of Adjuvant Therapy in the East

Principles

Due to results of several clinical trials [1–3], it is widely accepted that good local control by either radiation therapy or surgery is essential to cure gastric cancer. D2 dissection provides better local control of gastric cancer than D1 or D1 + radiation [4, 5]. High incidence of nodal disease in gastric cancer occurs in relatively early stage tumor as well, which justifies prophylactic application of D2 lymphadenectomy for stage IB or more advanced tumors [6].

Standard of Care in the Eastern Asian Countries

D2 dissection is widely accepted as common practice without serious increase of mortality with limited increase of morbidity in the East, due to high volume of patients with gastric cancer in each institution. Based on this surgical practice, adjuvant treatment does not include radiation therapy. Based on the results of two pivotal studies in this area [7, 8], postoperative adjuvant chemotherapy is the standard of care.

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The advantage of postoperative setting of adjuvant treatment is that unnecessary toxic treatment can be avoided for patients who do not need any adjuvant treatment (stage I). This was a weak point of pre- or perioperative adjuvant treatment. In the MAGIC study of perioperative chemotherapy, 8.3 % of patients in surgery alone arm had T1 tumor, suggesting that similar proportion of patients in the peri-operative chemotherapy group were overtreated by unnecessary toxic agents [9]. Good prognosis of stage I patients after surgery alone means probability of occult residual cancer cells, which are target of adjuvant treatment, is very low (less than 10 %) in these patients [10]. Unlike Western countries, proportion of stage I patients in Korea and Japan is more than 50 %, thus this concept is quite important for patients and medical economy [11, 12].

Standard Regimen of Postoperative Chemotherapy

The adjuvant chemotherapy trial of TS-1 for gastric cancer (ACTS-GC) study showed significantly better overall survival (OS) and relapse-free survival (RFS) of the patients with stage II and III (Japanese classification [13]) gastric cancer using TS-1 monotherapy than surgery alone. Hazard ratio (HR) was 0.669 (95 % CI:0.540–0.828) for whole patients and that was 0.509, 0.708, 0.791 for stage II, IIIA, IIIB patients, respectively [8]. This monotherapy reduced mainly peritoneal (HR: 0.687) and nodal + local

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recurrence (0.505) but not remarkably distant metastasis (HR: 0.86). Based on these results, S-1 monotherapy is widely accepted in East Asian countries as one of the standard adjuvant treatment.

CLASSIC study showed significantly better disease-free survival (DFS) and OS for stage II and III (UICC TNM classification [14]) using XELODA + oxaliplatin (XELOX). HR of DFS was 0.56 (95% CI: 0.44–0.72) for whole patients and that was 0.55, 0.57, 0.57 for stage II, IIIA, IIIB patients, respectively [7]. These results were confirmed after 5-year follow up [15]. The HR of OS was 0.66 (95CI: 0.51–0.85) for whole population and 0.54, 0.75, and 0.67 for stage II, IIIA, IIIB, respectively. The HR of DFS was 0.58 (95% CI: 0.48–0.72). This doublet chemotherapy reduced mainly hematogenous (HR: 0.61) and nodal + local (HR: 0.51) but not peritoneal recurrence (HR: 0.87), which makes clear contrast with TS-1 monotherapy. Based on these results, XELOX is one of the standard treatments in Korea, China, and Taiwan. This study has two weak points: First, high proportion of patients did not receive allocated treatment (11% in surgery alone arm and 19% in chemotherapy arm) and secondly unusually large number of censored cases are seen in survival curves (both OS and DFS), suggesting lack of robustness of the statistical analyses.

Remaining Clinical Questions

1. Is stronger or more intensive adjuvant treatment more efficient?
   Since there was a tendency of worse HR with more advanced stage in the ACTS-GC study, more intensive treatment is searched for stage III patients. Theoretically, more intensive and therefore stronger chemotherapy might be better than single agent therapy, but expected worse feasibility (tolerance) of such treatment after D2 gastrectomy might ruin chemotherapeutic effect.
2. Can OS be improved by adding preoperative chemotherapy to postoperative chemotherapy?
   Advantage and disadvantage of preoperative chemotherapy (neoadjuvant chemotherapy (NAC)) is shown in Table 22.1. Unlike colon cancer, disturbance of oral intake is prominent after surgery in gastric cancer patients. Therefore, the most important benefit of NAC is high tolerability of rather intensive treatment, using multiple drugs. Another important benefit of NAC in gastric cancer is related with higher incidence of surgical complications

Table 22.1 Neoadjuvant versus postop adjuvant

	NAC	Postop adjuvant
Primary lesion	Expecting shrinkage	Resected
	Delayed resection	Early resection
	Minimal spillage	Spillage of tumor cells
Micrometastasis	Early treatment	Delayed treatment
	Less influence by surgery	Growth stimulation by surgery?
Macroscopic metastasis	M1 possible	Only micrometastasis
Tumor burden	Large tumor burden	Minimum tumor burden
Drug delivery	Better	Reduced
Judgment of efficacy	Always evaluable	Impossible
Selection of pts	Less information	Maximum information
Compliance of CTX	High	Low
Influence to surgery	Growth during CTX	No influence
	Toxicity may cancel surgery	
	Toxicity may delay surgery	
	Potential increase of morbidity	
	Potential increase of mortality	

which may hamper early start of adjuvant chemotherapy than in colorectal cancer.

3. Is there any role of radiation therapy added to chemotherapy after D2 surgery?
   The update analysis of INT0116 study showed that chemoradiotherapy in this trial reduced mainly local regional recurrence but not systemic recurrence. These data support the finding that this treatment is effective after D0/1 surgery but not after D2 surgery [16]. After the results of INT0116 study were published, a Korean group performed a phase III study to compare adjuvant chemoradiation with surgery with chemotherapy (XELOX) alone (ARTIST trial) [17]. Although there was a subgroup in which borderline benefit of this treatment was suggested, primary endpoints did not meet [17]. Chemoradiation after D2 surgery was not accepted as efficient adjuvant treatment for gastric cancer but there remains a question about role of radiation therapy after D2 surgery in advanced stage.

Ongoing Phase III Clinical Trials in Asia to Solve these Questions (Table 22.2)

1. Comparing two adjuvant chemotherapy after D2 surgery
   a. S-1 + oxaliplatin (SOX) versus S-1 (POTENT study)
   b. Capecitabine + oxaliplatin (XELOX) versus XELOX + docetaxel
   c. S-1 versus S-1 + docetaxel
2. Evaluation of additional effect of NAC
   a. NAC by docetaxel + SOX followed by adjuvant S-1 after D2 surgery versus S-1 adjuvant after D2 surgery
   b. NAC by SOX followed by SOX after D2 versus SOX after D2

Table 22.2 Recent randomized trials for neoadjuvant and adjuvant chemotherapy

Number in the text	Trial registration number	Control arm	Test arm 1	Test arm 2	Country	Sponsor
1-a) POTENT	NCT01795027	S-1	SOX		China	University
1-b)	NCT01935778	XELOX	XELOX + Doc		Korea	Hospital
1-c) START-2	UMIN000010337	S-1	S-1 + Doc		Japan	Cooperative Group
2-a) PRODIDY	NCT01515748	S-1	NAC by DSOX + surgery + S-1 (post)		Korea	Drug company
2-b) RESONANCE	NCT01583361	SOX	NAC by SOX + surgery + SOX		China	Hospital
2-c)	NCT01534546	XELOX	SOX	NAC by SOX + surgery + SOX + S-1	China	University
2-d)	NCT01665274	XELOX	NAC by XELOX + surgery + XELOX		China	University
3-a) ARTIST II	NCT01761461	SOX	S-1	SOX + S-1 with radiation + SOX	Korea	Hospital
3-b)	NCT01815853	Periop XELOX	Preop CRT (XELOX) + surgery + XELOX		China	University
3-c)	NCT01711242	XELOX	XELOX with radiation		China	University

CRT chemoradiation therapy

   c. NAC by SOX followed by SOX after D2 followed by S-1 versus SOX after D2 versus XELOX after D2
   d. NAC by XELOX followed by XELOX after D2 versus XELOX after D2
3. Role of radiation therapy added to adjuvant chemotherapy
   a. Surgery + S-1 versus surgery + SOX versus surgery + SOX + radiation (ARTIST II trial)
   b. NAC by XELOX + surgery followed by XELOX with or without concurrent preoperative radiotherapy
   c. Surgery + XELOX with radiation versus XELOX

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Radiation Treatment for Gastric Cancer

23

Carla Hajj and Karyn A. Goodman

Introduction

The mainstay of therapy for gastric cancer remains surgical resection; however, once the disease has spread through the submucosa, the risk of lymph node involvement increases and the likelihood of 5-year overall survival drops to 20–30 % [1, 2]. Local or regional recurrence in the gastric or tumor bed, the anastomosis, or regional lymph nodes occurs in 40–65 % of patients after gastric resection with curative intent [3–6]. Most patients are not cured by surgery alone and, despite widespread acceptance of the benefits of adjuvant therapy; there is no currently recognized standard combined multimodality regimen, particularly in countries where D2 resections are routinely performed. Nearly every combination of adjuvant therapy to surgery can be justified. In this chapter, we will focus on the role of radiation treatment in the setting of surgically resectable locally advanced gastric cancer.

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Adjuvant Chemoradiotherapy

The Gastric Surgical Adjuvant Trial (INT-0116) [7] was a randomized phase III trial initiated in 1991, after prior adjuvant therapy trials had not resulted in higher survival rates than surgery alone. Patients were enrolled after a margin-negative resection for adenocarcinoma of the stomach or gastroesophageal junction (GEJ). Gastric resection with an extensive (D2) lymphadenectomy was recommended, but patients were not excluded on the basis of the extent of lymph node dissection. After a review of the surgical records, only 54 (10 %) patients had undergone a formal D2 dissection. A D1 dissection (removal of all invaded lymph nodes) had been performed in 199 patients (36 %), and most patients (54 %) had undergone a D0 resection, which is less than a complete dissection of the involved nodes.

A total of 556 patients were randomly assigned to surgery plus postoperative chemoradiotherapy (281 patients) or surgery alone (275 patients). The adjuvant treatment consisted of 425 mg/m^2 body-surface area/day of fluorouracil plus 20 mg/m^2 body-surface area/day of leucovorin for 5 days, followed by radiation treatment given with modified doses of fluorouracil and leucovorin on the first four and the last 3 days of radiotherapy. One month after the completion of radiotherapy, two 5-day cycles of fluorouracil (425 mg/m^2/day) plus leucovorin (20 mg/m^2/day) were given 1 month apart.

Chemoradiotherapy consisted of 4500 cGy in 180 cGy fractions over 25 fractions. The radiotherapy fields included the tumor bed and regional nodes, including the perigastric, celiac, local

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paraaortic, splenic, hepatoduodenal or hepatic-portal, and pancreaticoduodenal lymph nodes. In patients with tumors of the GEJ, paracardial and paraesophageal lymph nodes were included in the radiation fields.

After a central review of the radiation treatment plans, 35% were found to contain major or minor deviations from the protocol, most of which were corrected prior to the start of the treatment. Nonetheless, the final central review showed major deviations in 6.5% of the treatment plans and suboptimal radiotherapy has been found to be associated with worse outcome. Poor compliance with the protocol treatment-planning recommendations may have reflected unfamiliarity with the postoperative abdominal anatomy, but may have also been due to concerns about potential toxicity associated with large fields [8].

In 2001, MacDonald et al. reported the results of INT0116, showing a clear survival advantage for the use of chemoradiation after resection for gastric cancer, supporting a major role for radiation therapy in the adjuvant treatment of this disease [7]. The patients included in this study had a high risk of locoregional failure (more than two thirds of the patients had stage T3 or T4 tumors, and 85% had nodal metastases). The median overall survival in the surgery-only group was 27 months, compared with 36 months in the chemoradiotherapy arm. Updated results with more than 10 years of follow-up demonstrated persistent benefit in progression-free and overall survival from adjuvant chemoradiotherapy [9]. The sites of local and regional relapse were respectively 2 and 22% in the treatment arm and 8 and 39% in the control arm, suggesting that adjuvant chemoradiotherapy sterilized subclinical locoregional failure sites that would otherwise have resulted in relapse and death. There was no statistical difference in the rates of distant recurrence between the two groups, suggesting that further improvements in overall survival will likely come from improvements in systemic disease control.

Only 64% of the patients completed their chemoradiotherapy as planned. Three patients (1%) died from toxic effects of the chemoradiotherapy; grade 3 toxic effects occurred in 41% of the patients in the chemoradiotherapy group, and grade 4 toxic effects occurred in 32%. Hematologic and gastrointestinal toxic effects predominated. Late toxicities including secondary malignancies appeared acceptable, given the magnitude of benefit in terms of locoregional control and overall survival. In the chemoradiation arm, there were 21 patients (representing 25 separate cancers) with second malignancies versus 8 in the observation group ($p = 0.21$).

This study established postoperative chemoradiotherapy as a standard of care for patients with resected stage IB through intravenous (IV) (M0), gastric or GEJ adenocarcinoma. The INT-0116 study also showed that D0 resection is the most common type of lymph node dissection performed in the USA during resection for gastric cancer. In their updated paper, the authors of the study commented that the "INT-0116 reflects the real world of gastric surgery in North America."

Even so, the major limitation for global acceptance of this study was the limited lymph node dissection (D0 or D1) performed in 90% of patients enrolled into the trial. D2 lymph node dissection entails resection of all perigastric lymph nodes and celiac, splenic or splenic-hilar, hepatic arterial and cardial lymph nodes depending on the location of the tumor and is the most common widely accepted surgical procedure in Asia and European countries.

Although one would imagine extensive lymphadenectomy to be beneficial in removing subclinical cancer, its value has not been proven for gastric cancer. To date, no phase 3 trial has demonstrated a survival benefit resulting from D2 nodal resection. The argument that postoperative radiotherapy compensates for suboptimal surgery has not been verified, in fact, a large Korean series has suggested that postoperative chemoradiotherapy in D2-resected gastric-cancer patients can prolong survival and decrease recurrence [10]. A group from Memorial Sloan Kettering Cancer Center (MSKCC) has also looked at the patterns of initial relapse in completely resected gastric adenocarcinoma. From July 1985 through June 2000, 1172 patients underwent an R0 resection. These patients were largely treated with an extended lymph node dissection (81% D2 or greater). Of the 1172 patients, 496 (42%) had recurrence and complete data on recurrence could be obtained in 367 patients (74%). A locoregional

failure was reported in 54% of patients. There was no locoregional failure reduction with D2 surgery [11].

Adjuvant Chemoradiotherapy Versus Chemotherapy Alone

Numerous meta-analyses have suggested a survival benefit associated with adjuvant chemotherapy in patients with gastric cancer [12–15]. The goal of the Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial was to compare postoperative treatment with capecitabine plus cisplatin (XP) versus XP plus radiotherapy (XRT) with capecitabine (XP/XRT/XP) [16]. Patients with stage II/III gastric cancer with curative R0 resection and extended D2 lymphadenectomy were randomized to adjuvant chemotherapy alone (six cycles of XP [capecitabine 2000 mg/m^2 per day on days 1–14 and cisplatin 60 mg/m^2 on day 1, repeated every 3 weeks] versus chemoradiotherapy [two cycles of XP followed by 45-Gy with capecitabine 1650 mg/m^2 per day for 5 weeks followed by two cycles of XP]). Patients with stage IA or IB (T2aN0) disease, microscopically positive resection margin, and involvement of M1 lymph nodes or distant metastases were excluded from the study.

The radiation treatment fields included the tumor bed, anastomotic site, duodenal stump, regional lymph nodes, and 2 cm beyond the proximal and distal margins of resection. The remnant stomach was not routinely included within the radiation target. Anterior-posterior parallel opposing fields were used. The prescription dose was 45 Gy delivered in 180 cGy per daily fraction over 5 weeks.

Rates of compliance were very high and treatment was completed as planned by 75.4% of patients (172 of 228) in the chemotherapy arm and 81.7% of patients (188 of 230) in the radiation arm. The most frequent treatment-related side effects requiring treatment modification was neutropenia (58 patients in the chemotherapy arm and 41 patients in the radiation arm).

After a median follow-up of 53.2 months, the estimated 3-year disease-free survival (DFS) rates were 78.2% in the radiation arm versus 74.2% in the chemotherapy arm, $p=0.0862$). The addition of chemoradiotherapy to XP chemotherapy did not significantly improve DFS. However, in the subgroup of patients with pathologic lymph node metastases at the time of surgery (396 patients, or 86%), the chemoradiotherapy arm had significantly better 3-year DFS compared with the chemotherapy-alone arm (77.5 versus 72.3%, $p=0.0365$), and the statistical significance was retained at multivariate analysis.

The role of postoperative radiation treatment in D2 resected gastric cancer has long been debated based on the hypothesis that D2 resection alone may be sufficient for locoregional control. Nonetheless, this study has shown that postoperative radiation treatment is well tolerated and associated with lower DFS rates in patients with pathologic lymph nodes after curative R0 resection and D2 lymphadenectomy.

These findings should be interpreted with caution since they were from a subgroup analysis. A subsequent trial (ARTIST-II) is planned in patients with lymph node-positive gastric cancer after D2 lymph node dissection.

Preoperative Chemoradiotherapy

Preoperative chemoradiotherapy is well established for esophageal and GEJ cancers; however, it has not been a standard approach for gastric tumors. Preoperative treatment facilitates tumor downstaging prior to resection and allows adjuvant treatment to be delivered when local tissue has been surgically undisturbed. In addition, the presence of an intact tumor facilitates the planning of more accurate and effective radiation fields. Finally, preoperative treatment provides a time window during which more aggressive cancers can declare themselves before a major surgery is undertaken. Phase II data from the M.D. Anderson Cancer Center have demonstrated excellent R0 resection rates and promising preliminary outcomes and toxicity profiles with preoperative chemoradiotherapy for gastric cancer [17]. Pathologic response rates following preoperative chemoradiotherapy are predictive of overall

survival in gastric cancer [18]. The Radiation Therapy Oncology Group (RTOG) performed a phase II study (RTOG 99-04) of preoperative chemoradiotherapy in patients with localized gastric adenocarcinoma [19].

Patients received two cycles of induction fluorouracil, leucovorin, and cisplatin followed by concurrent radiation and chemotherapy. The radiation fields encompassed the entire stomach, any perigastric extension, and the gastric, celiac, porta hepatis, gastroduodenal, splenic, supra pancreatic, and retro pancreaticoduodenal lymph nodes. For lesions involving the cardia or GEJ, a 5-cm margin of esophagus was included, and for distal lesions near the gastroduodenal junction a 5-cm margin of duodenum was included. The prescription dose was 45 Gy delivered in 180 cGy daily fractions over 5 weeks using the three-dimensional (3D) conformal radiotherapy technique. Concurrent chemotherapy consisted of 300 mg/m^2/day infusional fluorouracil and paclitaxel 45 mg/m^2 intravenously was administered each Monday for 5 weeks. Resection was attempted 5–6 weeks after chemoradiotherapy was completed. If a patient had an R0 resection, no further therapy was administered. In the case of an R1 resection, an R2 resection or M1 carcinoma, patients received palliative care.

Twenty institutions participated in this trial. Forty-nine patients were enrolled in this study and 43 (88%) patients were assessable. Of the 32 patients with sufficient anatomic information regarding the extent of their lymphadenectomy, 16 (50%) had a D2 dissection. The proportions of patients with stage IB, II, and III disease were, respectively, 12, 37, and 52%. The pCR and R0 resection rates were 26 and 77%, respectively. The quality of surgery improved, with 50% of patients undergoing D2 dissections, probably because surgery was part of this trial. At a median follow-up of 21.6 months, the median survival was 23.2 months and 1-year overall survival was 72%. R0 resection resulted in a favorable overall survival. Eighteen major radiotherapy protocol variations occurred, the majority due to field-size reduction to minimize toxicity per the discretion of the treating radiation oncologist. Grade 4 toxicity was reported in 21% patients and there were no treatment-related deaths. Given the promising results of the various sequences of adjuvant therapy, a randomized trial should be designed to compare preoperative to postoperative chemoradiotherapy in patients with gastric cancer.

Perioperative Chemotherapy with or Without Radiation Treatment

Although several Phase III randomized trials [20, 21] and a meta-analysis [22] of all published trials have shown no beneficial effect of preoperative chemotherapy, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial established preoperative and postoperative epirubicin–cisplatin–fluorouracil (ECF) chemotherapy as an acceptable standard therapy for resectable lower esophageal and stomach cancer [23].

In the MAGIC trial, chemotherapy consisted of three preoperative and three postoperative cycles of intravenous epirubicin (50 mg per square meter of body-surface area) and cisplatin (60 mg per square meter) on day 1, and a continuous intravenous infusion of fluorouracil (200 mg/m^2/d) for 21 days. Patients were randomized to either perioperative chemotherapy and surgery (250 patients) or surgery alone (253 patients). The resected tumors were significantly smaller and less advanced in the perioperative-chemotherapy group. With a median follow-up of 4 years, the perioperative chemotherapy group had significantly higher overall survival and progression-free survival rates than the surgery group. The 5-year survival rates were 36 and 23%, respectively, in the perioperative chemotherapy and surgery groups ($p=0.009$). Most tumors were in the distal stomach, but 25% of the patients had lesion in the esophagus or the GEJ. Forty-two patients had a D2 dissection. Only 42% of patients completed all chemotherapy.

The Chemoradiotherapy After Induction Chemotherapy of Cancer in the Stomach (CRITICS) trial, is currently investigating perioperative treatment with epirubicin, cisplatin, and capecitabine chemotherapy alone versus epirubicin, cisplatin, and capecitabine chemotherapy followed by concurrent chemoradiotherapy with 45 Gy over 5

weeks and weekly cisplatin and daily capecitabine in patients with gastric cancer after D1 or greater resection. This study is expanding on the MAGIC protocol and asking whether there is additional benefit to postoperative chemoradiotherapy.

The Trial of preoperative therapy for gastric and esophagogastric junction adenocarcinoma (TOPGEAR) trial is an international randomized phase III trial of preoperative chemoradiotherapy versus preoperative chemotherapy for resectable gastric cancer. It is an intergroup trial led by the Australasian Gastro-Intestinal Trials Group (AGITG), in collaboration with the Trans Tasman Radiation Oncology Group (TROG), the European Organisation for Research and Treatment of Cancer (EORTC), and the National Cancer Institute of Canada (NCIC) Clinical Trials Group currently assessing the role of perioperative chemotherapy with or without preoperative radiation treatment. Patients with resectable adenocarcinoma of the stomach or GEJ will be randomized to receive either preoperative chemotherapy alone (3 cycles of ECF as per the MAGIC trial regimen) or preoperative chemoradiotherapy (2 cycles of ECF followed by 45 Gy of radiation given concurrently with 5-fluorouracil). Following surgery, both groups will receive three additional cycles of ECF. The trial is being conducted in two parts. Part I (Phase II component) will recruit 120 patients with the aim of showing trial feasibility and sufficient efficacy and safety of preoperative chemoradiotherapy. Part II (Phase III component) will recruit an additional 632 patients to provide a total of 752. The primary endpoint for Part I is pathological complete response rate, and for Part 2 it is overall survival. The trial includes formal quality of life and biological sub-studies. In addition, the trial incorporates a rigorous quality assurance program that includes real-time central review of radiotherapy plans and central review of surgical technique.

Managing Gastric Versus GEJ Tumors

The decision-making process for the management of gastric cancer has become more complex since nearly every combination of adjuvant therapy to surgery has been justified. The seventh edition of the American Joint Cancer Committee/Union Internationale Contre le Cancer AJCC/IUCC staging manual for esophagus cancer has recently classified all GEJ cancers with an epicenter within the proximal 5 cm of the stomach in the same category as distal esophageal cancers [24]. The clinical characteristics, biologic behavior, and survival after esophagectomy are similar for adenocarcinoma of the GEJ and distal esophagus [25]. Siewert I and II are managed with preoperative radiation guidelines applicable to esophageal cancers per the NCCN guidelines. The NCCN guidelines state that Siewert III tumors may be treated either like gastric or like esophageal tumors depending on the clinical scenario. At MSKCC, Siewert III tumors are typically treated like gastric cancer.

If a patient is started on induction chemotherapy per the MAGIC protocol, radiation treatment is generally omitted and patients are only sent to see the radiation oncologist on a case-by-case basis. If patients undergo upfront surgical resection, postoperative chemoradiotherapy based on the INT 0116 trial is usually recommended. Both approaches can be justified and the optimal timing of radiation with respect to surgery still needs to be defined. Both the MAGIC and the INT 0116 show similar benefit with a hazard ratio of approximately 0.75. The population is slightly different in the INT 0116 trial as patients were randomized after R0 resection, as opposed to the MAGIC trial where patients were randomized before surgery. In the USA, surgeons tend to operate right away so the patients included in the INT 0116 study are more likely to be representative of the general population of gastric cancer.

The standard at MSKCC for gastric cancer is to prefer perioperative chemotherapy, per the MAGIC trial, and to consider radiation treatment in case of positive margins or positive lymph nodes without a significant response to preoperative chemotherapy. The preferred chemotherapy regimen is epirubicin, oxaliplatin (EOX) instead of ECF. Adjuvant chemoradiation treatment may also be offered to patients with locally advanced gastric adenocarcinoma (i.e., pT3, pT4, or pN +

disease). Preoperative chemoradiation treatment is not typically used at our institution in the absence of randomized controlled studies to support this approach.

Radiotherapy Planning and Techniques

Radiation treatment for gastric cancer can be technically challenging and associated with significant toxicities. The radiation oncologist should be familiar with the proper techniques of radiation delivery to either the primary tumor or the operative bed. Moreover, the maintenance of adequate nutrition during therapy and supportive care are critical. Treatment interruptions or dose reductions for manageable acute toxicities should be avoided.

Patients should undergo a CT scan for radiation-treatment planning and are positioned supine with arms up in an immobilization device for reproducibility of daily set-up. Typically, the patient should fast 2–3 h prior to simulation with daily treatment to achieve reproducibility of the remnant stomach and/or bowel filling. When clinically appropriate, IV and oral contrast should be used. The IV contrast is useful for the delineation of the lymph nodes and the oral contrast aids in the delineation of the esophagus, gastric remnant, and duodenal stump.

At MSKCC, patients are treated using intensity-modulated radiation therapy (IMRT), which allows selective delivery of high doses of radiation to the region of interest with steep dose gradients at the transition to adjacent normal tissues such as the heart, lungs, kidneys, and liver (Fig. 23.1). The use of 3D radiotherapy and IMRT is actually strongly encouraged by the NCCN.

One major challenge in treating gastric cancer either pre- or postoperatively is that the abdominal contents move with respiration, with excursions of greater than 2 cm in the cranio-caudal direction. In the past, this has necessitated large margins around the tumor or postoperative bed to account for motion. More recently, there are novel motion-management techniques to account for respiratory motion, such as respiratory gating. Respiratory gating allows for reduction in the treatment margin and the consequent radiation exposure to normal tissues, thereby limiting treatment-related toxicities [26] by just turning the radiation beam on at a certain time during the breathing cycle when the tumor or postoperative bed is in a certain position. To facilitate confirmation that the radiation beam is turning on at the appropriate time during the respiratory cycle, radio-opaque markers or operative clips can be visualized on daily pretreatment x-rays to confirm that the position of the tumor or postoperative bed is in the treatment field.

The clinical target volume for adjuvant radiation treatment for gastric cancer depends on the location of the primary disease as well as the status of the lymph nodes involved by disease. Diverse and widespread patterns of direct extension and lymphatic drainage oblige the radiation oncologist to treat very large fields to cover areas of potential relapse and high rates of acute and late toxicity. In addition, older studies such as the INT 0116 were conducted in the era of 2D planning, commonly involving anterior–posterior opposed fields, leading to unnecessary irradiation of large volumes of highly sensitive abdominal organs. Consequently, studies have explored the feasibility and safety of 3D conformal radiation treatment and IMRT [27–30]. The type of operation depends on the location and extent of the primary tumor. For proximal cancers involving the cardia or the proximal third of the stomach, a total gastrectomy with Roux-en-Y esophagogastrectomy is indicated. During this type of procedure, the right and left gastric arteries are dissected at their respective bases, and the entire stomach is removed from the GEJ to the duodenum just below the pylorus. For distal cancers involving the antrum, pylorus, or distal third of the stomach, a subtotal gastrectomy is adequate. During this type of surgery, the left gastric artery is often dissected at its base. However, in contrast to a total gastrectomy, because the proximal stomach is left intact in this case, the right paracardial and left paracardial nodes and portions of the lesser curvature and greater curvature lymph nodes are not surgically dissected [31].

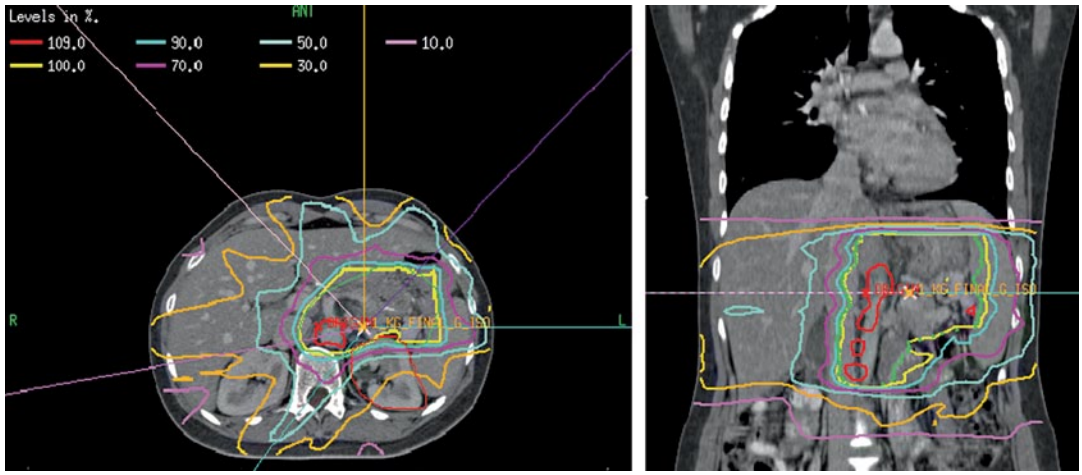

Fig. 23.1 Axial and coronal views of a radiotherapy plan showing the isodose lines to deliver the high dose to the postoperative bed and regional nodes and limiting the radiation dose to the normal structures

The nodal sites to include in the target volume depend on the T- and N-stage and on the location of the primary tumor. In case the lymph nodes are pathologically negative for disease (pN0), covering the perigastric lymph nodes is recommended. For pT4b disease, nodes related to the sites of adherence should also be included. In the case that the lymph nodes are pathologically involved with disease (pN+), then the nodal coverage will depend on the site of the primary tumor in the stomach. For proximal tumors, including the perigastric, celiac, and splenic lymph nodes is recommended. The pancreaticoduodenal, porta hepatic, periesophageal, and mediastinal nodes could also be included at the discretion of the physician. For distal tumors, including the perigastric, celiac, pancreaticoduodenal, porta hepatic, and splenic nodes is recommended. The splenic hilum could also be included. The planning target volume is delineated by adding margins to the clinical target volume to account for organ motion and setup uncertainties. The target is usually large and results in the inclusion of significant portion of the kidney, bowel, and liver.

The prescription dose is 45 Gy given in 180 cGy per daily fraction, with a cone down to 50.4–54 Gy in 180 cGy per fraction to any residual disease. Radiotherapy is given concurrently with capecitabine or infusional 5-fluorouracil.

Conclusions

In summary, radiotherapy remains part of the armamentarium of adjuvant therapy options for gastric cancer. Significant advances have been made in radiation planning and delivery which may impact on the ability to deliver abdominal radiotherapy with greater efficacy while minimizing toxicity. Ongoing clinical trials will further elucidate the role of radiotherapy in gastric cancer and help to define risk groups who may benefit most from this therapy.

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Targeted Therapy and Novel Agents for the Treatment of Gastric Cancer: A View Toward the Future

24

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Introduction

Gastric cancer is an aggressive disease and although its incidence has declined, still remains the fourth most common type of cancer and the second leading cause of cancer-related death around the world [1]. Surgical approach is the only potential curative treatment, but despite optimization of surgery (R0 resection), radiotherapy, and cytotoxic chemotherapy, the 5-year survival rate is really poor [1].

It is reported that each year 900,000 patients are diagnosed with this disease [1]. Potentially, approximately 25 % of these patients may benefit by adding trastuzumab to current standard treatment. The 5-year survival rate after R0 resection and adjuvant multimodal treatment is approximately 40 %. Despite adjuvant perioperative chemotherapy for stages II and III, the overall treatment failure rate measured as 5-year recurrence or death rate is over 60 % in Western patients. Similarly poor are the results from the USA despite standardization of adjuvant chemoradiotherapy. The higher 5-year survival rate of 60 % in Japan as compared to the Western world can be explained by standardization of D2 lymphadenectomy in Japan and differences in tumor biology [2, 3].

Targeted therapy provides the potential for improving oncological outcomes [4]. Over the past decade, several agents targeting key components of important downstream signaling have been developed and approved by the Food and Drug Administration (FDA) for a series of cancers [4]. In this way, the latest deeper understanding of molecular "pathways" involved in many types of cancers shaping the way for the discovery of novel exciting targeted therapies [5].

In this chapter, we address with the latest scientific information on targeted drugs for the treatment of this aggressive disease and we provide a view toward the future on this issue.

Gastric Cancer Guidelines

Gastric cancer is the fourth most common cause of death from cancer worldwide. Undoubtedly, accurate tumor staging is essential for prognostic purposes. Recently, the Japanese Gastric Cancer Association (JGCA) published new versions of the guidelines. In western countries, the tumor-

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node-metastasis (TNM) system has been proposed by both the International Union against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Nowadays, there has been an agreement between the TNM categories in the new JGCA and the UICC/TNM seventh edition system. The most relevant modifications were the adoption of the classification proposed by the TNM and a simplification of the definitions for the types of lymphadenectomy. An important aspect to keep in mind is that the UICC, the AJCC, and the JGCA have made a great effort toward the establishment of a common "language" for gastric cancer treatment [6, 7].

This common language includes that endoscopic mucosal resection is recommended for patients with Tis or T1a tumors [7, 8]. Moreover, surgery is the cornerstone of treatment for T1b-2 stage or higher and any N stage. Adequate gastrectomy is recommended for T1b-3 tumors, while T4 tumors require resection of involved structures. As for D2, lymph node dissection has undoubtedly been the standard procedure for curable gastric cancer in eastern Asia for many years. On the other hand, in western countries and in the USA, D2 only recently became a recommended surgical option [9].

Another critical area is chemotherapy. The Japanese guidelines are different from the European and American (National Comprehensive Cancer Network [NCCN]) guidelines [10]. In adjuvant chemotherapy, S-1 is strongly recommended in Japan in patients with stage II or III gastric cancer following D2 gastrectomy. In the ACTS-GC trial, S-1 patients demonstrated significantly better survival than those undergoing surgery alone. In the west, surgery alone is considered an insufficient treatment for most patients [11]. NCCN recommends, in accordance with the results of the MAGIC trial, perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil regimen or its modifications for patients with T2 or higher and any N tumors (category 1 of evidence). Moreover, preoperative chemoradiation may also be evaluated for these patients (category 2B of evidence). For patients who have not received preoperative therapy, postoperative chemoradiation (5-fluorouracil ± leucovorin or capecitabine before and after fluoropyrimidine-based chemoradiation) is recommended for selected patients (T3 and 4, any N and T2N0 patients with poorly differentiated tumors, lymphatic invasion, and neural invasion and age younger than 50 years) [10]. In addition, based on the results of the CLASSIC trial in the east, postoperative chemotherapy is included with capecitabine and oxaliplatin after D2 gastrectomy in patients with T3, T4, and any N tumor. Moreover, for M1 or unresectable tumors docetaxel, cisplatin, and fluorouracil regimen or its modifications is recommended by NCCN, while in Japan the S-1 plus cisplatin regimen is widely used [10, 12].

Trastuzumab with active chemotherapy is considered for HER2/neu-positive patients [13, 14]. In order to highlight the existing differences, we can mention that survival in western countries seems improved after adjuvant chemoradiation therapy and neoadjuvant chemotherapy, while this evidence is not yet established in Japan. Despite the differences in treatment, management, and chemotherapy regimens for gastric cancer between Japan and the west, the different biological behavior of the tumors seems to influence the overall survival of these patients. Biological and oncological differences of gastric cancer in East Asia and the western world can be explained by genetic variation among populations and whole-genome function. The interpretation of genetic variants in patients with gastric cancer should be within the context of the local geographic genetic background [7, 15].

The ERBB/HER/EGFR Epidermal Growth Factor Receptor Family

The discovery of the epidermal growth factor (EGF) and its receptor (EGFR) in 1962 and 1978, respectively, opened the way for a new era of molecular oncology [16]. However, successful translation of these basic research findings into the clinic has occurred only during the past decade. The ERBB/HER or epidermal growth factor receptor (EGFR) family is represented by 4 receptor tyrosine kinases with similar architectural properties. Notably, these 4 kinases are HER1 (EGFR), HER2, HER3, and HER4, each comprising an extracellular ligand binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain [16, 17]. Ligand

binding to the extracellular domain of EGFR results in either homodimerization (binding to another EGFR) or heterodimerization (binding to another member of the ERBB family). It is reported that normal expression of EGFR is seen in intestinal and renal tissue, while overexpression has been documented in many tumor types [16].

Notably, EGFR overexpression has been demonstrated up to 44 % of gastric cancers, with rates increasing to up to 64 % with proximity to the gastroesophageal junction, where it is reported to be associated with poorly differentiated histology, increased invasion, and worse prognosis. HER2 amplification and overexpression plays a central role in initiation, progression, and metastasis of breast and gastric cancer [17]. HER2 status has been recognized as an important prognostic factor. Patients with breast cancer or gastric cancer and HER2-positive disease have significantly worse survival than those with HER2-negative tumors. Thus, this important receptor is a potential therapeutic target and in this way, the crucial activity of the EGF receptor family may be significantly inhibited by extracellular or intracellular "block" by novel sophisticated agents [17, 18]. Notably, monoclonal antibodies (mAbs) targeted against the extracellular binding site inhibit ligand binding and subsequent activation of the intracellular tyrosine kinase domain. On the other hand, tyrosine kinase inhibitors (TKIs) of the EGFR pathway exhibit activity in the intracellular domain of the receptor, by blocking the ATP-binding site [17, 19].

Anti-EGFR mAbs

We highlight that till date 3 mAbs (cetuximab, panitumumab, and matuzumab) targeting EGFR have been evaluated in clinical trials for patients with gastric cancer.

Cetuximab (Erbitux ®, Imclone Systems, NY, USA)

It is reported that cetuximab is a partially humanized murine anti-EGFR mAb. This agent is approved by FDA for the treatment of irinotecan refractory metastatic colorectal cancer. This drug has been studied in several phase II nonrandomized trials in combination with standard cytotoxic chemotherapy as first-line treatment for advanced gastric cancer [20]. These studies have reported overall survival (OS) rates ranging from 9 to 16 months. The randomized phase II CALGB80403/ECOG 1206 study compared the addition of cetuximab to three cytotoxic chemotherapy regimens (irinotecan–cisplatin, folinic acid–fluorouracil–oxaliplatin [FOLFOX], and epirubicin–cisplatin–fluorouracil) in patients with advanced esophagogastric cancer. Both ECF-C and FOLFOX-C demonstrated response rates of > 50 % and comparable overall survival, however, FOLFOX-C had a decreased rate of ≥ grade 3 toxicity when compared with ECF-C (78 vs. 61 %). OS observed was not significantly greater than that observed in studies evaluating these chemotherapy regimens alone [21]. In comparison with cetuximab, the anti-EGFR mAbs matuzumab and panitumumab have both been associated with potentially decreased efficacy and increased toxicity when added to cytotoxic chemotherapy for advanced gastric cancer [22].

Markers of Response to Cetuximab

The relationship between EGFR expression in gastric cancer and response to cetuximab remains unclear: two trials with folinic acid–fluorouracil–irinotecan (FOLFIRI), and FOLFOX chemotherapy demonstrated no correlation between EGFR positivity and response to cetuximab, whereas a trial with FOLFOX demonstrated an overall response rate (ORR) of 100 % for patients with EGFR expression [23]. However, in colorectal cancer, overexpression of EGFR by immunohistochemistry has failed to be predictive of potential benefit of either cetuximab or panitumumab. Furthermore, in contrast to colorectal cancer, where *K-Ras* mutation occurs in 40 % of patients and correlates robustly with no response to cetuximab and panitumumab, the presence of a *K-Ras* mutation is rare in gastric cancer and has not been associated with resistance to these agents [24].

Matuzumab (EMD72000, Merck)

The randomized phase II MATRIX trial examined the addition of matuzumab, a humanized anti-EGFR mAb to epirubicin–cisplatin–capecitabine (ECX) chemotherapy in the first-line treatment of advanced esophagogastric cancer [25]. A nonsignificant trend was seen toward worse progression-free survival (PFS) and OS in the matuzumab-ECX group (4.8 vs. 7.1 months) and (9.4 vs. 12.2 months), respectively, underlying the need to evaluate the effect of new agents added to conventional chemotherapy in the setting of a randomized, controlled trial [25].

Anti-EGFR Tyrosine Kinase Inhibitors (Erlotinib-Gefitinib)

Erlotinib (Tarceva®, Genentech, CA, USA) and gefitinib (Iressa®, AstraZeneca, London, UK) are orally available TKIs targeting the EGFR, and both of them have been approved for the treatment of metastatic non-small-cell lung cancer, where responses are more common in patients with activating mutations of the *EGFR* gene [26]. In addition, erlotinib has also been licensed for the treatment of pancreatic cancer in combination with gemcitabine chemotherapy regimen.

Both agents have been evaluated in treating advanced gastric cancer with controversial and nonpositive results. Of 30 patients with advanced early gastric cancer treated with erlotinib in a phase II second-line setting, only two responses were reported, both in EGFR-positive squamous cell carcinoma [27]. Moreover, median time to progression in adenocarcinoma was only 1.6 months. In the first-line setting, single-agent erlotinib had an ORR of 0% in gastric and 9% in gastroesophageal junction adenocarcinomas, with median OS of 4 and 7 months in these groups, respectively [28]. Similarly, gefitinib in the first-and second-line setting has demonstrated ORR of only 3–11% and median OS of 4–6 months. For these reasons, it is more than clear that till date neither erlotinib nor gefitinib have significant activity in advanced gastric cancer [29].

Targeting HER2 in Gastric Cancer: Current Evidence

Recently more than 35 anticancer targeted drugs have been approved by the FDA, and about 150 agents are in preclinical and clinical staging, aiming at the discovery of more effective therapies [30].

In the vast majority, these anticancer agents target a single specific mutation or gene amplification. By inhibiting deregulated single-cellular signaling pathways, such agents can restore pathologic cell proliferation, survival, growth, apoptosis, invasion, angiogenesis, metabolism, and metastasis, which are thought to be the hallmarks of cancer [31]. Despite the explosion in the single-gene-targeting approach, with intensive research efforts and major investment by the pharmaceutical industry and the public sector, the efficacy of these single signaling transduction pathway inhibitors is in most cases modest. This is translated into a few weeks or months survival prolongation in the metastatic setting, which is not surprising if we consider substantial limitations of currently available targeting therapies [32].

The reasons for high intrinsic and acquired resistance rates to available targeting drugs include their temporary antitumor activity, lack of consideration of interpatient and intratumor heterogeneity, little attention to dynamics of transcriptional circuitry, and lack of a comprehensive view on how the cancer genome structure and molecular networks drive gene expression regulation [33].

The most important of these agents is now trastuzumab [34].

Trastuzumab (Herceptin®, Genentech): A Translational Triumph

It is out of question that targeted therapy represents the major hope in the "war" against cancer and a substantial step toward personalized medicine. An overenthusiasm and explosion in drug development followed the evidence of clinical success with trastuzumab [35].

HER2 (ERBB2) is variably overexpressed in gastric cancer; it is described that expression is highest in tumors of the gastroesophageal junction (>20–30%), lowest in diffuse-type tumors (6%), and intermediate (10–15%) in intestinal-type tumors of the distal stomach [36].

Trastuzumab is a fully humanized mAb that binds to the extracellular domain of the receptor, acting by blockage of the HER2 receptor, inhibition of dimerization, as well as by the induction of antibody-dependent cellular cytotoxicity (ADCC), and increasing endocytosis of the receptor and possibly through antiangiogenic effects [37]. It was developed in the 1990s, after murine monoclonal antibodies directed to the extracellular domain of HER2 were produced and evaluated in cell lines and xenografts [38].

Clinical Data

Although information on the specific genetic pathways involved is poor, HER2 has been shown to be amplified and overexpressed in gastric cancer. Notably, HER2 is progressively considered by the researchers as an important biomarker in gastric cancer, with studies pointing out amplification or overexpression in 7–34% of tumors, mainly in the intestinal type and in esophagogastric junction and proximal tumors [39].

Cortés-Funes et al. presented preliminary results of a phase II study involving 21 chemotherapy-naïve patients with HER2 overexpressing locally advanced or metastatic gastric cancer. Trastuzumab at a loading dose of 8 mg/kg and maintenance dose of 6 mg/kg and cisplatin 75 mg/m^2 were administered every 21 days until progression, unacceptable toxicity, or withdrawal of consent. Response rate was of 35%, with 17% of patients achieving stabilization. The tolerability profile was favorable; no grade 4 toxicity was observed and mostly the frequent grade 3 events were asthenia, nausea or vomiting, diarrhea, hiporexia, and neutropenia. Data from another preliminary phase II study involving 16 gastric cancer patients were presented by Egamberdiev et al. Trastuzumab 6 mg/kg was administered once in addition to cisplatin 100 mg/m^2 during 3 days + fluorouracil (5-FU) 1000 mg/m2 3 days + leicovirin 100 mg/m^2 3 days, every 3 week. Authors reported an objective response rate of 54.5% in the combined therapy group vs. 33.3% in the chemotherapy-only group and a median remission duration of 8.3 months vs. 5.2 months. In a recent phase II study carried out by Grávalos et al., chemo-naïve patients with nonresectable advanced or metastatic gastric or esophagogastric adenocarcinoma overexpressing HER2 were treated with trastuzumab 8 mg/kg as loading dose and 6 mg/kg in subsequent cycles + cisplatin 75 mg/m^2 every 3 weeks. Twenty-two out of 228 patients (9.6%) enrolled had HER2 overexpression. An overall response rate of 32% was found, with disease control achieved in 64% of patients; median time to progression was 5.1 months. No grade 4 toxicities occurred, whereas most frequent grade 3 adverse events were asthenia, neutropenia, anorexia, diarrhea, and abdominal pain. Interestingly, higher baseline HER2 extracellular domain levels associated with better response to therapy. In more recent studies, HER2 overexpression was found to be lower than previously reported, especially in distant gastric cancers. Resectable gastric cancer has reported HER2-positive ratios of 8.1 and 11.7%, suggesting that in resectable gastric cancer HER2 positive status might be less frequent than in advanced gastric cancer [40, 41].

The ToGA Trial: A Milestone in Modern Oncology

The phase III ToGA trial [14] constitutes a milestone in modern oncology, establishing trastuzumab as the first biological therapy with demonstrated survival benefits in gastric cancer. In this way, ToGA trial was a multicenter, international trial, performed in 24 countries. It evaluated the combination of trastuzumab with standard chemotherapy (cisplatin + either capecitabine or 5-FU) in advanced (inoperable locally advanced, recurrent, or metastatic) HER2-positive gastric cancer as a first-line therapy vs. chemotherapy alone. Patients enrolled were treated with six cycles of chemotherapy in both treatment arms, with patients in the experimental arm continuing to be treated with trastuzumab until disease progression. Cisplatin 80 mg/m^2 was given on day 1 by intravenous infusion. Capecitabine 1000 mg/

m^2 was given orally twice a day for 2 weeks followed by a 1-week rest or 5-FU 800 mg/m^2 per day was given by continuous infusion on days 1–5 of each cycle. Trastuzumab was given intravenously at a loading dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg afterward. The primary endpoint of the study was to compare OS in both arms, and the secondary endpoints were to compare progression-free survival (PFS), time to progression, overall response rate, disease control, duration of response, and quality of life between the two arms. It is important to highlight that in this "historical" trial, among approximately 3670 tumor tissue specimens screened for HER2 positivity, 22% were revealed HER2 positive (34% of the intestinal type vs. 6% of diffuse and 20% of mixed types). The highest rate was observed in 34% of esophagogastric junction cancer and 20% of gastric cancer samples. The researchers reported that the combination of trastuzumab with chemotherapy in advanced HER2-positive gastric cancer patients showed significantly better OS rates compared to the same chemotherapeutic regimen alone (median OS in the combination treatment group was 13.8 months vs. 11.1 months in the chemotherapy-alone arm). This effect was observed in patients with intestinal type gastric cancer but not in those with diffuse type gastric cancer. Median PFS (6.7 months vs. 5.5 months) and radiological response rate (47 vs. 35%,) was also revealed improved with trastuzumab therapy. In fact, patients with strongest HER2 expression gained the greatest benefit, with a median survival of 17.9 months in patients treated with trastuzumab against 12.3 months which received chemotherapy alone [14].

As for the adjuvant setting, it is important to consider the possible benefits of trastuzumab in the adjuvant setting for earlier stages of the disease. Important trials have been conducted with the intent to investigate anti-HER2 therapeutics in this setting. Early onset gastric cancer (presenting at or under the age of 45) seems to have lower HER2 overexpression than in late onset cases, with possible different molecular genetic pathways [14].

Based on these results, trastuzumab has been licensed and approved for the treatment of advanced gastric cancer in the USA and Europe [14].

Limitations

The absolute benefit in response rate to trastuzumab addition to chemotherapy was 12.8% and it resulted in a prolongation of overall survival by 2.4 months. These data indicate resistance to trastuzumab even among HER2-positive selected patients. However, it is likely that, because of less residual disease after surgery in resectable gastric cancer, the trastuzumab therapeutic gain may be larger in the adjuvant setting with substantial 5-year survival rate benefit [42].

However, the absolute survival benefit is small because resistance and relapse or disease progression rates with fatal outcome still remain high. Exciting research has focused on understanding molecular mechanisms underlying this resistance, aiming to develop novel, more effective drugs with higher clinical response rates [42].

Overcoming Resistance

Resistance to molecular targeting therapy is currently the cause of treatment failure in cancer. Similarly, the absolute additional response rate to trastuzumab among HER2-positive advanced gastric cancer in the ToGA study is small: 12.8%. Given that HER2-positive accounts for approximately 25%, only 3.12% of all gastric cancer patients can benefit from trastuzumab treatment [42].

Trastuzumab Emtansine (T-DM1)

The single agent T-DM1 is an ADC that incorporates the HER2-targeted antitumor capacities of trastuzumab with the cytotoxic properties of the microtubule-inhibitory agent DM1 (derivative of maytansine); the antibody and the cytotoxic agent are described to be conjugated by a stable linker. Interestingly, T-DM1 allows intracellular drug delivery specifically to HER2-overexpressing cells, thereby improving the therapeu-

tic rate and minimizing the exposure of normal tissue cells to the complex. It seems that T-DM1 is internalized upon binding to HER2-overexpressing tumor cells. Moreover, it is the first HER2-targeted ADC with a stable and unique linker. T-DM1 is an ADC that is currently being investigated in various clinical trials. Early in its development, studies were conducted to identify the optimal linker to conjugate trastuzumab to DM1. Interestingly, in preclinical studies, it was shown that linking DM1 to trastuzumab via a nonreducible thioether yielded superior activity, improved pharmacokinetics, and presented less toxicity compared with trastuzumab linked to a maytansinoid via a disulfide linker. Furthermore, the T-DM1 was shown to be selective for HER2-positive cells, displayed enhanced potency compared with trastuzumab alone in vitro, and retained activity against trastuzumab-resistant cells in vitro and in vivo. In other words, T-DM1 is an agent that combines an antibody and a cytotoxic agent, which are conjugated by means of a stable linker. A trial is now underway to examine the efficacy and safety of T-DM1 compared with standard taxane therapy in patients with HER2-positive gastric cancer. In this study, patients will be randomized to one of three groups, 3.6 mg/kg T-DM1 every 3 weeks, 2.4 mg/kg T-DM1 every week, or standard taxane therapy, for at least four cycles (12 weeks). The endpoints include overall survival, progression free survival, duration of response, and time to gastric cancer symptom progression, as well as safety. The near future will determine the exact role of T-DM1 in the current therapeutic "armamentarium" for HER2 positive gastric cancer [42, 43].

Anti-HER2 Tyrosine Kinase Inhibitors

Lapatinib (Tykerb ®, Glaxosmithkline)

Other HER2 targeting agents have also been developed, including lapatinib. Lapatinib is an orally active synthetic drug that is approved for HER2-positive breast cancer in combination with capecitabine. Lapatinib inhibits HER2 signaling by blocking tyrosine kinase activity. In the lapatinib with paclitaxel (Taxol) in Asian HER2 Gastric Cancer Study (TYTAN), for example, patients across five Asian countries are to be randomly assigned to lapatinib (1500 mg daily) plus paclitaxel (80 mg/m^2 weekly) or paclitaxel alone. The primary endpoint of the study is OS. This study did not show an improvement in the primary endpoint. However, the efficacy of lapatinib was strongly suggested in the IHC3 subset. These results indicate that the definition of HER2-positive gastric cancer is very important for the development of new anti-HER2 drugs. As mentioned above, lapatinib is an oral TKI with activity against EGFR and HER2/neu and is licensed for the treatment of HER2 refractory breast cancer. Results from the use of this agent in gastric cancer have not been promising to date. Lapatinib was evaluated as a single agent in an unselected advanced gastric cancer patient population in the first-line treatment setting. In this study (SWOG S041), a confirmed partial response rate of only 7% was seen, and median OS was 5 months, which compares unfavorably with standard cytotoxic chemotherapy. A study of single-agent lapatinib in 25 previously treated patients selected by EGFR or HER2 positivity by IHC or FISH (HER2 only) demonstrated an ORR of 0% and stable disease in two patients only. Further evaluation of lapatinib in HER2-positive patients in the phase III setting is ongoing in two trials: the LOGIC trial (NCT0068090), evaluating capecitabine and oxaliplatin with or without lapatinib, and the TYTAN trial, evaluating second-line paclitaxel with or without lapatinib (NCT00486954) [44, 45].

Antiangiogenetic Strategies for Gastric Cancer

Tumor angiogenesis and metastasis are robustly associated with angiogenesis in most solid tumors. Recognition of the vascular endothelial growth factor (VEGF) pathway as a key regulator of angiogenesis has led to the development of several VEGF-targeting agents, including

neutralizing antibodies to VEGF or its receptor (VEGFR) and TKIs targeting the VEGFR. New blood vessel formation or neovascularization is crucial for tumor growth and metastasis. VEGF is the most potent mediator of this process. VEGF binds to the high-affinity receptors VEGFR (type 1 and 2) and leads to endothelial cell migration and proliferation and changes in the extracellular matrix resulting in increased vascular permeability and sustained new blood vessel formation. Antiangiogenesis strategies using both mAbs and TKIs have improved OS in several tumors types such as colon, renal, non-small-cell lung cancer, and hepatocellular carcinoma, and have been extensively evaluated in gastric cancer. In gastric cancer setting, it is reported that increased tumor and serum VEGF levels are associated with a poor prognosis [46, 47].

Anti-VEGF mAb Therapy

Bevacizumab (Avastin ®, Genentech)

It is widely known that bevacizumab is a humanized anti-VEGF mAb that is approved for the treatment of metastatic colorectal cancer, breast cancer, renal cell carcinoma, non-small-cell lung cancer, and glioblastoma. There are various promising phase II studies that have evaluated the addition of bevacizumab to first-line chemotherapy in advanced gastric cancer with OS rates reported of up to 17 months. As for phase III trials, the large randomized phase III AVAGAST trial compared the addition of bevacizumab to a cisplatin/fluoropyrimidine doublet in approximately 780 patients receiving first-line treatment for gastric cancer. The researchers reported discouraging results. OS was 10.1 vs. 12.2 months in the chemotherapy-alone and chemotherapy plus bevacizumab groups respectively (HR: 0.87; $p=0.1002$). PFS and antitumor response were significantly improved in the bevacizumab-containing arm with response rates increasing from 37 to 46% and PFS from 5.3 to 6.7 months with the addition of this agent [48–53].

Tyrosine Kinase Inhibitors of Angiogenesis

TKIs of angiogenesis, which have demonstrated efficacy in renal cell and hepatocellular carcinoma, are also under investigation in gastric cancer.

Sunitinib (Sutent ®, Pfizer, NY, USA)

Multi-TKI sunitinib has exhibited activity against VEGFRs as well as Raf, platelet-derived growth factor receptor beta, fibroblast growth factor receptors, and c-KIT. At present, sunitinib at 50 mg/day as a single agent has been studied as a second- or third-line treatment for advanced gastric cancer in two nonrandomized phase II studies. An Asian study showed a partial response rate of 2.6% and a >6-week stable disease rate of 32.1%, while the median PFS was 2.3 months and median OS was 6.8 months. In another phase II trial, sunitinib monotherapy was conducted on 52 patients with chemorefractory advanced gastric cancer, resulting in a median OS of 5.8 months and displaying less effectiveness. Although sunitinib was well tolerated in these pretreated patients, these studies showed little clinical value in a monotherapy setting. Thus, a randomized trial of second-line chemotherapy plus sunitinib versus chemotherapy alone is necessary to establish the therapeutic benefit of sunitinib in this pretreated patient population. A randomized phase II trial of FOLFIRI chemotherapy with or without sunitinib in the second-line setting is ongoing (NCT01020630) [54].

Sorafenib (Nexavar ®, Bayer, Germany)

Sorafenib is a potent inhibitor of the Raf tyrosine kinase as well as several other receptor tyrosine kinases involved in the progression of gastric cancers, such as VEGFR-2 and VEGFR-3. Based on data derived from hepatocellular carcinoma trials, several studies were designed to investigate the role of sorafenib in advanced gastric cancer. In a first phase II study ($n=44$) for patients with metastatic (80%) or locally advanced

(20%) gastric and esophagogastric junction cancer using oral sorafenib (400 mg twice daily) in combination with docetaxel and cisplatin in a 21-day cycle, the median OS was 13.6 months, with a PFS of 5.8 months and a response rate of 41%. The authors supported that sorafenib combined with docetaxel and cisplatin was effective and tolerable as a treatment for gastric cancer. The addition of sorafenib to cisplatin/docetaxel chemotherapy led to an ORR of 41% and stable disease in a further 31% of patients, with tolerable toxicity. Median OS was reported at 12.6 months. A dose-finding study of sorafenib plus cisplatin/capecitabine in 21 locally advanced or metastatic gastric cancer patients achieved similarly encouraging results, with an ORR of 62% and PFS median OS of 10 and 14.7 months, respectively [55–57].

Other Targets in Gastric Cancer

Although agents targeting members of the ERBB/HER family and tumor angiogenesis in gastric cancer have received the most attention to date, there are multiple potential targets under investigation. The mTOR/PI3K pathway, known to be upregulated in gastric cancer, has been successfully targeted in renal cell carcinoma and neuroendocrine tumors.

Everolimus

Everolimus (RAD001) is an oral inhibitor of mammalian target of rapamycin, which is downstream of the Akt pathway. The results of a phase II study of everolimus in 53 patients with previously treated AGC showed a disease control rate of 56.0% and median PFS of 2.7 months. At a median follow-up duration of 9.6 months, the median OS was 10.1 months and good tolerability was observed. After obtaining a remarkable response in patients with metastatic gastric cancer in previous phase I/II studies in Japan, a prospective randomized placebo-controlled study evaluating the efficacy of everolimus as a second- or third-line therapy in 656 patients with advanced gastric cancer was conducted. Although the PFS was significantly improved by everolimus (1.7 months vs. placebo, 1.4 months; $p < 0.0001$), the OS, a primary endpoint of the study, was not significantly different (everolimus, 5.4 months vs. placebo, 4.3 months; $p = 0.1244$) [58].

Challenges and Future Prospects

Emerging data from the clinical development of molecular-targeted agents have provided novel opportunities that are expected to translate into survival benefits in the treatment of advanced gastric cancer. The final results of the ToGA study [14] recently demonstrated that the addition of trastuzumab to combination chemotherapy can achieve important survival advantages in patients with HER2-positive gastric cancer. However, this benefit is limited to only ~20% of patients (patients with HER2-positive advanced gastric cancer). Therefore, there remains a critical need for both the development of more effective agents and the identification of predictive and prognostic molecular markers to select those patients who will benefit most from specific chemotherapeutic regimens and targeted therapies. The epidemiology, pathology, and behavior of proximal, distal, and diffuse gastric cancers are distinct, as evidenced by the variable expression of HER2 according to gastric cancer subtype. These differences are represented by unique molecular phenotypes in which differentially expressed genes may serve as potential targets for novel therapies. The greatest challenge for the future will be the identification of multitargeted agents given in combination with or without conventional cytotoxic chemotherapy [42, 59, 60].

A View Toward the Future

All the researchers agree that the 1000 Genome Project using NGS now marks the new era of personal whole-genome analysis. This international consortium was designed to answer a “big” question: how do genome sequences differ among people from distinct geographical areas and

ancestry, and what genomic differences affect human disease? For the first time, this large-scale genomic study in 1092 individuals from 14 populations around the world provided enormous data: 38 million single nucleotide polymorphisms, 1.4 million short insertions and deletions, and approximately 14,000 larger deletions [61]. The study provides evidence that individuals from different populations carry different profiles of rare and common variants. The implication of the 1000 Genome Project data is that the interpretation of rare variants in individuals with a particular disease should be within the context of the local geographic-based genetic background [62]. Based on this resource, new studies may reveal underlying rare genetic variations distinct for gastric cancer in East Asia and the western world explaining the increased tumor aggressiveness and poor survival seen in the USA and Europe as compared with China, Japan, and Korea [7, 10].

Treatment of gastric cancer and gastrointestinal tumors generally has been improved over the past two decades. Particularly laparoscopic surgery has improved short-term outcomes and quality of life with less pain, shorter hospital stay, and better cosmesis [7, 63, 64]. However, little progress has been made in advanced disease and other tumors with high treatment failure rates. Beyond the 1000 Genome Project, the Encyclopedia of DNA Elements project has being mapping the functional components of the human genome using high-throughput NGS methods. These two international, large-scale projects have changed biomedical research on human biology and genome organization. These latest data, pave now the direction of medicine, specifically cancer prevention and therapy, by setting the genomic basis of human disease and cancer [65, 66]. A new era has been started to identify inherited and somatic point mutations and larger structural changes across the human genome. The next and much more exciting challenge is to unravel how genetic and epigenetic aberrations at the genome scale affect and perturb regulatory cancer networks, molecular circuits, and signaling pathways in cancer [67]. Understanding the organizational principles underlying human genome control and cell function represents the most rational way for improving prevention and therapy of gastric cancer [68].

Moving from cell lines to biological samples, such as blood and tissue, in the application of NGS will provide crucial insights into how inherited and somatic variations affect regulatory DNA and transcriptional regulatory networks that drive gene expression and cell control in health and disease. It is probable that point mutations and larger structural changes along with epigenome aberrations may differ between gastric cancer in the east and west. In this case, management and therapeutic approaches may require a specific geographical strategy [69].

A future goal with highly effective drug combinations on the basis of personal mutational landscape and transcriptome architecture is the next-generation genome diagnostics-based therapeutics [70, 71].

Breakthrough sequencing technologies reveal nowadays the importance not only of protein-coding sequences for identifying intragenetic variation but also noncoding, regulatory natural variants which affect transcription and gene expression, ensuring biodiversity in human physiology and evolution [72–75]. Genome-wide association studies have shown that most (approximately 88 %) of disease-associated variants in susceptibility loci are within the noncoding region of the human genome [76]. Therefore, protein-coding and noncoding mapping of the genome using next-generation sequencing technologies for whole-genome sequencing/whole-exome sequencing and RNA sequencing can dramatically improve our understanding of cancer [77–80]. Understanding interindividual genetic variation, diversity, and heterogeneity as a cause of diversity in phenotypes and interpatient tumor genetic and genomic mutational heterogeneity, or both coding and noncoding DNA and RNA is crucial for understanding, preventing, and "fight" cancer [81].

However, the current high-throughput sequencing-based confirmation of the previous concept of clonal mutation evolution, interpatient, and intratumor diversity/heterogeneity increases in a dramatic way the challenge in how to predict tumor responsiveness and select the best

possible therapeutic agent combination treatment for each patient. However, this is not the only problem in the effort to reach robust personalized treatment [82–84]. Beyond a patient's mutational landscape assessment, the next challenge is to understand how this heterogeneous genomic aberration affects individual genome function, cellular signaling networks, and gene expression regulation [85]. There is now a clear consensus that personalized clinical medicine is much more complex than it was first thought. Understanding transcriptional circuitry, driving gene expression regulation, represents a daunting challenge which requires innovative developments in both technologies and methods. New exciting research efforts are emerging in exploring genome-wide molecular mechanisms regulating gene expression and are behind cancer cell progression and metastasis [86]. Now, in the post-ENCODE era, breakthrough technologies including high-throughput sequencing and arrays, as well as living-cell imaging techniques, including visualization of interacting molecules using biosensors coupled with novel computational and mathematical approaches, allow the study of molecular interactions, transcriptional circuitry, and gene expression regulation through intracellular signaling networks [87]. As we are now moving away from the standard, linear approach of simplified single-gene transcription-dominated human biology and medicine, which lasted ~60 years, to a much more complex transcriptional network driving gene regulation, the new post-ENCODE age of genome network medicine (GNM) is just now beginning [88]. The objective of GNM is patient-derived sampling analysis for biospecimen-based cancer genome architecture in large-scale international genomic studies [89]. It is expected that these patient-derived genomics will not only complete the genetic mutations catalog for each cancer type but also can provide revolutionary information on how mutational and epigenetics genome-wide landscape affects transcriptional regulatory networks, gene function, and cancer cell metastatic capacity. Although this goal appears overambitious and very difficult to reach, it is perhaps the "only" way to dramatically improve cancer patient outcome [90]. This rational network-based approach, combining advances in genome science and network biology, provides high hopes for the future development of robust biomarkers for assessing sensitivity or resistance to available agents and the discovery of next-generation, network-based drugs [91].

Conclusion

Although trastuzumab has been established as standard treatment in advanced or metastatic HER2 positive gastric cancer and we hope similar efficacy in the adjuvant setting, therapeutic resistance-based recurrence and disease progression will continue to be a major clinical problem. T-DMI can further improve survival of HER2 positive patients but the results of phase III RCTs should be awaited before clinical use.

All available targeted drugs, including trastuzumab, have been developed on the basis of single linear transcription traditional view. However, all these drugs are limited by their temporary and moderate efficacy.

In the new post-ENCODE era we can hope toward the development of transcriptional networks-based next generation drugs.

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