

# Gastric cancer treatment in the world: Germany

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**Abstract:** Epidemiologically, around 15,500 persons per year contract gastric cancer with continuously decreasing incidence and a 5-year survival rate of only 30% to 35%. Contrary to the Asian countries, there are no prevention programs for gastric cancer in Germany, which leads to the disease frequently being diagnosed in locally advanced stages and predominantly being treated with multimodal therapy concepts. Complete (R0) resection is the therapy of choice for resectable gastric cancer. Special forms of gastric cancer that are limited to the mucosa can be endoscopically resected with a curative intent. Systematic D2 lymphadenectomy (LAD) plays a decisive role in the management of local advanced tumors because it significantly contributes to the reduction of tumor-related death and both local and regional relapse rates. Perioperative chemotherapy improves prognosis in the advanced stages, whereas palliative chemotherapy is normally indicated for metastatic diseases. Standardized resection procedures and the use of individualized multimodal therapy concepts have led to improvement in the 5-year survival rate.

**Keywords:** Gastric cancer; Germany; current treatment; prognosis

Received: 27 March 2017; Accepted: 04 May 2017; Published: 26 May 2017.

doi: 10.21037/tgh.2017.05.07

View this article at: <http://dx.doi.org/10.21037/tgh.2017.05.07>

## Introduction

Although the incidence of gastric cancer is continuously decreasing worldwide, more than 15,500 new gastric cancer diagnoses were recorded in Germany in 2012 (1). The decreasing incidence is especially attributed to a balanced diet, improved food preservation processes, and tobacco smoking abstinence. Based on the statistics from the Robert Koch Institute, 9,978 deaths associated with new cases of malignant stomach diseases were documented in Germany in 2012, with a West-East gradient in terms of incidence (1). In Germany, the tumors found in more than half of the patients during the first diagnosis are already in locally advanced or disseminated stages. Only a small percentage

of gastric cancers are diagnosed in the early stages (~10–20%) in Germany compared with that in certain Asian countries with systematic prevention programs, such as South Korea and Japan (2,3). Furthermore, no significant improvement in the overall survival rate has been achieved despite standardized surgical procedures and reduction in postoperative morbidity and mortality rates. The overall 5-year survival rate for all tumor stages is 30–35% (1).

## Diagnostics and staging

Esophagogastroduodenoscopy is the most prioritized method among all the gastric cancer diagnostic techniques. This examination method is used to detect tumors and

has higher sensitivity and specificity in diagnosing upper digestive tract neoplasms than the other diagnostic techniques. Multiple targeted biopsies should be conducted if a neoplasm is suspected (4). Meanwhile, endoscopic ultrasound and computed tomography (CT) should be performed to assess local tumor infiltration as well as local and regional involvement (5). Endoscopic ultrasound examination is not necessary if local endoscopic resection is planned. However, endosonography is useful in distinguishing T1/2 from T3/4 cancers. A B-mode ultrasound examination with sensitivity and specificity of 53–81% and 60–98%, respectively, can be performed to detect liver metastases and gastroesophageal junction adenocarcinomas for the exclusion of cervical lymph node metastasis (6). CT of the abdomen and thorax should be conducted to exclude distant metastases and gastroesophageal junction cancer. If locally advanced T3/4 cancer is found, staging can be improved by performing diagnostic laparoscopy, in order to exclude small liver metastases or local peritoneal cancer (7).

### Current treatment

Endoscopic resection procedures with a curative treatment approach can only be used in mucosal carcinoma (8). Primary surgical therapy is performed in the case of a locally limited tumor (cT1b/cT2), whereas perioperative chemotherapy should supplement surgical therapy after the exclusion of distant metastases and peritoneal carcinosis if there is a locally advanced tumor (cT3 or more). Furthermore, initiation of palliative chemotherapy is indicated for a tumor in a metastasized stage. In the case of obstruction, perforation, or hemorrhage related to an advanced tumor condition, individual interventional or surgical therapy (resection/bypass/stenting) should be considered. Meanwhile, curative follow-up resection should be performed if R1 or R2 is observed after tumor resection in a curative setting; otherwise, combined radiochemotherapy can be carried out (4,9).

### Surgery

#### *Endoscopic treatment*

The applicability of an endoscopic resection with a curative approach for a tumor depends on the extent of tumor infiltration and likelihood of the occurrence of lymph node metastasis. One must consider the possibility of 3–6%

lymph node involvement if the tumor is limited to the mucosa and up to 20% if infiltration into the submucosa takes place (10). Based on the Japanese gastric cancer classification, tumors with the following features are classified as “low risk”: mucosal carcinoma, <2-cm raised-type lesion, <1-cm flat-type lesion, G1/G2 grade, absence of macroscopic ulceration, L0 and V0 invasion stage, and intestinal carcinoma. Considering the low frequency of gastric cancer in the early stage in Germany, en bloc resection should only be performed by endoscopists with expertise. Local therapy measures for cancer that meet the “expanded criteria” remain to be fully established. After complete endoscopic resection, endoscopic follow-up is recommended at an interval of every 3 months in the first year, every 6 months in the second year, and once a year thereafter (4,11,12).

#### *Minimally invasive surgery (MIS)*

The importance of MIS, specifically laparoscopic surgery, in the management of gastric cancer is controversial despite the fact that this technique has been established as a standard procedure for benign tumors and gastrointestinal stromal tumors based on the current study results. The studies and meta-analyses on gastric cancer thus far have predominantly been performed in Asia and have shown the advantages of MIS with regard to intra-operative blood loss, minor surgical complications, and rapid convalescence, although this method has no benefit or disadvantage in terms of long-term oncological results and quality-of-life improvement (13,14). In contrast to the situation in Germany, patients with gastric cancer in Asia are treated in high-volume centers, with early-stage cancer and predominantly distal tumor localization having a high incidence rate of 50% (3). Considering the marginal advantages of MIS compared with open resection as shown in published studies, no general recommendations for laparoscopic surgery of gastric cancer are currently established (15). In recent years, robot-assisted surgery, especially for gastric cancer, has been explored in most Asian centers, in addition to laparoscopy. However, the results showed that robotic surgery did not have any advantage over laparoscopic gastrectomy, and so far, this surgical approach had only been used in elective centers owing to its very high cost (16).

#### *Conventional surgery*

Standardization of surgical therapy for gastric cancer in

Germany was made possible based on the results of the German Gastric Cancer Study, which was carried out in the early 1990s (17), and the East German Gastric Cancer Study, which was performed around 10 years later (18). Today, systematic D2 lymphadenectomy (LAD) with the goal of complete (R0) resection, which is dependent on tumor localization and histological findings, is a generally recognized standard procedure. A comparison between subtotal distal and total gastrectomies, which considered the corresponding oral safety distances, revealed the absence of significant differences in postoperative morbidity or mortality and overall survival rates between the two approaches (19). R0 resection is achieved using a proximal safety distance of 8 and 5 cm in situ in the cases of diffuse-type lesion and intestinal carcinoma, respectively. With this approach, subtotal distal gastrectomy is carried out oncologically in the distal portion of the stomach for both early-stage cancer types (e.g., cT1b) and in the middle third of the stomach for advanced intestinal carcinoma. Gastrectomy is carried out in all the remaining cases. Total gastrectomy must be extended with transhiatal resection of the distal portion of the esophagus in adenocarcinoma of the esophagogastric junction (types 2 and 3 based on Siewert classification) (20). The extent of the extraluminal resection is determined very decisively through the removal of the locoregional lymphatic drainage areas. At least 25 lymph nodes are required for adequate LAD of compartments 1 and 2 based on the current guideline (3). The long-term results of the Dutch Gastric Cancer Study proved with certainty that D2 LAD had an oncological advantage over D1 LAD with limited radiality (21). Splenectomy and/or left pancreatic resection is only advisable in the case of direct infiltration of these organs or possible metastasis of the lymph nodes in the splenic hilum area. In the case of suspected infiltration of the neighboring organs, multivisceral resection is only advisable if an R0 situation can be achieved (20).

The performance of a reconstruction procedure is determined based on the surgeon's individual experience and respective prognosis assessment because an "optimum" reconstruction cannot be defined due to a lack of evidence in the existing studies. Roux-en-Y jejunal loop obstruction with gastrojejunostomy should be considered as the procedure of choice after subtotal distal gastric resection, which is also the most frequently carried out procedure worldwide after total gastrectomy. Other options, such as interposition of the jejunum or colon with duodenal involvement or the use of a pouch, with potential

postoperative advantages are also possible (22).

## Multimodal treatment

### *Perioperative chemotherapy*

The question of at which tumor stage should perioperative therapy be indicated remains to be fully elucidated (23). Two randomized phase III studies (Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) study, n=503; Fédération Nationale des Centres de Lutte Contre le Cancer/Francophone de Cancérologie Digestive (FNCLCC/FFCD) study, n=224) from Great Britain and France proved the benefits of perioperative chemotherapy on locally advanced gastric cancer. In both studies, the administration of 5-FU/cisplatin-based chemotherapy showed a marked survival advantage compared with surgery alone (24,25). In the MAGIC study, the 5-year survival rates after perioperative chemotherapy significantly increased in the groups where the participants underwent surgery alone (23%) and received perioperative chemotherapy (36%). This positive finding was confirmed by the result of the French FNCLCC/FFCD (38% *vs.* 24%). The results of both studies formed the basis for the currently valid guideline recommendation in Germany, despite their weaknesses in terms of methods and lack of adequate surgical quality control. Recently, the regimens discussed earlier have been replaced by the perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) regimen. This combination has already succeeded in reducing the histopathological remission rate; however, the complete survival data associated with this regimen remains to be obtained (26). A disagreement regarding T2 cancer management exists because the majority of the tumors analyzed in the studies were T3 tumors. For T2 tumors, the probability of the occurrence of lymph node metastases is approximately 50%. Thus far, no certain advantage of neoadjuvant therapy has been found for cT2N0 patients. Given that the use of lymph node size as an indicator of lymph node metastasis is unreliable, the lymph node status cannot be predicted with certainty in primary staging using endosonography and CT (27). Therefore, the S3 guideline only provides "can" recommendations for the indication of perioperative chemotherapy in cT2 tumors (4). The effectiveness of perioperative chemotherapy in a subgroup of patients with signet ring cell carcinoma is controversially discussed. Some evidences showed that signet ring cell carcinoma did not respond to regular chemotherapy

regimens; therefore, primary surgery should be performed. So far, the existing related prospective trials are yet to report their results (28).

### *Neoadjuvant radiochemotherapy*

Neoadjuvant radiochemotherapy is not indicated for primary resectable gastric cancer. Any valid statement cannot be made based on the available data because of small case numbers and lack of a control group. Furthermore, the therapeutic modality to be selected for locally advanced adenocarcinoma of the esophagogastric junction is still a subject of controversy (29). Preoperative chemotherapy and radiochemotherapy for locally advanced tumors are currently considered equivalent by the guideline experts (4).

### *Adjuvant chemotherapy*

The concepts of adjuvant therapy are not used in the development of standard treatment in Germany, in contrast to Asia and North America. Thus far, the results of the meta-analyses showed that adjuvant chemotherapy had an overall small but statistically significant survival advantage (4–6%), although this advantage was larger for patients with advanced tumors (30). However, this survival advantage was only proven through the meta-analyses of Western studies. Hence, adjuvant chemotherapy is currently only used in individual cases as a therapy option in patients with gastric cancer (e.g., after an emergency operation or in the case of indefinite staging) (4).

### *Adjuvant radiochemotherapy*

In a large study by the Southwest Oncology Group that involved 556 patients, McDonald *et al.* compared the outcomes of postoperative radiochemotherapy (4 cycles of 5-FU and leucovorin and 45 Gy radiochemotherapy) with those of surgical intervention alone (31). After an average follow-up observation period of 5 years, the results of this study revealed that postoperative radiochemotherapy had significant advantages in terms of average survival time lengthening of up to 9 months (27 *vs.* 36 months) as well as in relapse-free survival and local tumor control compared with surgery alone. However, these survival rates are a subject of controversy, especially due to the inadequate number of surgeries performed (<10% D2 resection). Therefore, postoperative radiochemotherapy cannot be generally recommended, but it can still be a therapy option

following interventions without D2 LAD (4).

### **Oligometastasis**

Palliative chemotherapy is usually recommended for metastatic patients. However, the new therapeutic concepts suggest the selection of stage IV patients who can benefit from surgery. Based on these concepts, surgery in a perioperative setting can be conducted in patients with potentially resectable oligometastasis in the liver, lung, lymph nodes or peritoneum (32).

### **Palliative chemotherapy**

Systematic chemotherapy was proven with certainty to be more advantageous than supportive measures. This therapeutic method not only improved the patient's general condition but also resulted in significant survival time improvement and quality-of-life maintenance (33).

### **Acknowledgements**

None.

### **Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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doi: 10.21037/tgh.2017.05.07

**Cite this article as:** Chon SH, Berlth F, Plum PS, Herbold T, Alakus H, Kleinert R, Moenig SP, Bruns CJ, Hoelscher AH, Meyer HJ. Gastric cancer treatment in the world: Germany. *Transl Gastroenterol Hepatol* 2017;2:53.