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## Treatment of early gastric cancer in the Western World

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West. Therefore the experience of endoscopic therapy or minimal invasive surgery is only in special centers available. Total or subtotal gastrectomy with D2-lymphadenectomy is the standard treatment for early gastric cancer with suspected lymph node metastases. Future studies including prediction of lymph node metastasis are necessary to optimize the therapy according to quality of life.

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## Abstract

The incidence rate of gastric cancer is much higher in Asia than in the Western industrial nations. According to the different screening programs in Japan and Korea about fifty percent of treated patients had an early tumor stage. In contrast, European and American patients with gastric cancer had an advanced tumor stage. Therefore, the experience for the various therapeutic options for gastric cancer may be different between these regions. In this review we tried to point out the treatment modalities in Western industrial countries for early gastric cancer.

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**Key words:** Gastric cancer; Early cancer; Epidemiology; Diagnosis; Therapy; Western World

**Core tip:** Early gastric cancer is a challenging disease with varying lymph node infiltration. In the Western industrial countries the frequency of early gastric cancer is much lower than in Asian countries. Especially, carcinomas limited to the mucosa are rare in the

## INTRODUCTION

Gastric cancer is the second most common cause of death from cancer worldwide<sup>[1]</sup>. Overall incidence rates for gastric cancer have steadily declined over the past 50 years, particularly in developed countries.

According to the Japanese classification of gastric cancer early gastric cancer (EGC) is defined as gastric cancer in which tumor invasion is confined to the mucosa or submucosa (T1 cancer), irrespective of the presence of lymph node metastasis<sup>[2]</sup>. Early gastric cancer carries a much more favourable prognosis than advanced cancer, with 5-year survival rates of over 90%<sup>[3]</sup>. A complete cure can almost always be achieved by conventional gastrectomy with lymph node dissection. Therefore, this treatment has been the gold standard, providing an excellent prognosis in patients with EGC in Eastern as well as in the Western world<sup>[3-5]</sup>. During the last years limited resection of the primary tumor and minimal invasive surgical approaches have been introduced for early gastric cancer<sup>[6]</sup>. On the other hand, endoscopic resection (ER) is beneficial, as it is minimally invasive and conserves the whole stomach, and postoperative quality of life is good<sup>[7,8]</sup>.

ER has been accepted as a minimally invasive treatment method for EGC with a negligible risk of lymph node metastasis. But according to the low frequency of EGC in the Western countries the experience with minimal invasive surgical and endoscopic methods are low compared to those in Asian countries.

The aim of this review is to show the actual knowledge about early gastric cancer in Western industrial countries.

## DEFINITION

The term “Early Gastric Cancer” is not really well defined. According to the Japanese classification of gastric cancer EGC is defined as gastric cancer in which tumor invasion is confined to the mucosa or submucosa (T1 cancer), irrespective of the presence of lymph node metastasis<sup>[2]</sup>. Sometimes it is used to contrast it to “Advanced Gastric Cancer”. In these cases, EGC includes T2 cancers in addition to T1 cancer. According to the 7<sup>th</sup> UICC-TNM classification T1 means the tumour has started to grow into the wall of the stomach. T1 is further divided into T1a and T1b. T1a means the tumour is within the inner layers of the stomach (the mucosa). And T1b means the tumour has grown through the mucosa and into a layer of supportive tissue called the submucosa<sup>[9]</sup>. The N-category describes the number of metastatic lymph nodes (LNM), N0 = no lymph node metastasis, N1 = 1-2 LNM, N2 = 3-6 LNM and N3 more than 6 LNM. The stage-system of the 7<sup>th</sup> UICC-TNM classification combined the T-, N-, and the M-category. Early gastric cancer is often used in the same manner as stage I tumor. In this stage system T1N0M0 (stage IA), T1N1M0 and T2N0M0 (stage IB) tumors are combined to stage I gastric cancer. T1N2M0 or T1N3M0 are classified to more advanced stages.

## EGC AND LYMPH NODE METASTASES

Hölscher *et al*<sup>[10]</sup> compared the frequency of LNM in patients with pT1 gastric cancer from Asian and European countries. In European countries there were 6.5% for mucosal carcinomas and 23.9% for submucosal carcinomas compared to 2.7% resp. 22.9% in Asian countries. Table 1 shows the results of literature for patients with pT1 gastric cancer in the Western countries<sup>[4,5,10,11-13]</sup>. One reason for the difference of LNM in pT1a cancer may be the higher frequency of tumor infiltration in the upper layer of the mucosa (m1 and m2) with no lymphatic invasion for Asian patients. The infiltration of the deepest layer (m3) represents an important step for a mucosal carcinoma. In the series from Hölscher *et al*<sup>[10]</sup> for German patients with mucosal carcinoma the rate of lymph node metastasis springs from 0% in m1 or m2 layers to 12.8% in m3 layer. Another reason for this dissimilarity may be different location of the primary tumor. Patients in Asian have more often tumor in the mid or lower third of the stomach compared to patients in Western countries with higher frequency of tumors in the proximal

third<sup>[16,17]</sup>. Further explanations, like biologic differences or differences in genomic or epigenomic changes, for differences in the frequency of LN metastasis between the two worlds are not really well studied and therefore topics of future studies.

## EPIDEMIOLOGY

Nearly for all countries in the world the incidence rate of gastric cancer declined during the last fifty years<sup>[1,18]</sup>. The main difference between Asian and Western industrial nations is the level of the incidence rate. Whereas in Japan an age standardized incidence rate (ASR) for males of about 80 per 100000 inhabitants were found in European countries the ASR for males is about 16 per 100000 inhabitants.

The frequencies of early gastric cancer in Western countries are not really known. According to the lower incidence rate of gastric cancer there exists no screening programs for this tumor entity. Faria *et al*<sup>[19]</sup> compared three decades in gastric cancer surgery in a Portuguese hospital and found an increase of EGC from 14.5% in the time span from 1980 to 1989 compared to 20.8% in the time span from 2000 to 2009. Data from Italian Research Group of Gastric Cancer showed a decreasing rate of patients with resected gastric cancer from 1991 to 2005 and during the same time span a decreasing rate of pT1 gastric cancer. But the rate of stage I carcinoma was not different in the three five years sections with 37.8%, 35.4% and 37.4%<sup>[20]</sup>. In Germany, there are three prospective multicenter observational studies: the German Gastric Cancer Study (GGCS ‘92) with data from 19 University hospitals in the time span 1986-1989, the quality assurance study of the East German study group for quality assurance and regional development in surgery (EGGCS ‘02) including the data from 2002 of 80 hospitals and the German multicenter observational studies for gastric cancer for surgical treatment of gastric cancer (QCGC 2007-2009) including the data from 2007-2009 of 141 hospitals<sup>[21-23]</sup>. Stage I gastric cancer was detected in 27.3% of all cases of GGCS ‘92, in 34.1% of EGGCS ‘02 and in 34.2% of cases from QCGC 2007-2009 study. But all these data are from surgical hospitals. During this time span the indication for surgery in advanced cases may be changed. On the other hand, patients with early cancer are more often treated by endoscopic resection. Therefore, it is not clear if the incidence of EGC has changed in the Western.

Based on data from population-based cancer registries the survival rate of Japanese patients with gastric cancer is higher in Japan than in Western countries. One reason may be the high rate of EGC as a consequence of the various screening programs. Other factors of influence like more radical therapy are discussed.

## THERAPEUTIC OPTIONS FOR EGC

Treatment options for early gastric cancer range from endoscopic mucosal resection (EMR), endoscopic sub-

**Table 1** Survey of the literature on the rate of lymph node metastasis in surgically resected mucosal or submucosal pT1 gastric cancer in Europe

| Ref.                                  | Year | Origin  | pT1a |       | pT1b |       |
|---------------------------------------|------|---------|------|-------|------|-------|
|                                       |      |         | n    | % LNM | n    | % LNM |
| Folli <i>et al</i> <sup>[11]</sup>    | 1995 | Italy   | 117  | 4     | 106  | 23    |
| Hayes <i>et al</i> <sup>[12]</sup>    | 1996 | Germany | 14   | 21    | 14   | 64    |
| Bösing <i>et al</i> <sup>[13]</sup>   | 1998 | Germany | 33   | 9     | 24   | 17    |
| Popiela <i>et al</i> <sup>[14]</sup>  | 2002 | Poland  | 113  | 6     | 125  | 21    |
| Roviello <i>et al</i> <sup>[15]</sup> | 2006 | Italy   | 330  | 5     | 322  | 24    |
| Hölscher <i>et al</i> <sup>[10]</sup> | 2009 | Germany | 47   | 11    | 79   | 25    |
| Nieminen <i>et al</i> <sup>[4]</sup>  | 2009 | Finland | 47   | 2     | 43   | 23    |
| Saragoni <i>et al</i> <sup>[5]</sup>  | 2013 | Italy   | 308  | 6     | 221  | 26    |
|                                       |      | Europe  | 1009 | 5.9   | 934  | 24.3  |

LNM: Lymph node metastasis.

mucosal dissection (ESD), laparoscopic or open distal gastric resection to gastrectomy with radical lymph node dissection.

EMR has become the standard of care for removal of large flat and sessile neoplastic lesions of the gastrointestinal tract in Japan and Korea. The applications of EMR and ESD are expanding and many Western endoscopists are adopting these techniques. But according to the low frequency of early gastric cancer in Western countries and the high frequency of lymph node metastases in those EGC the standard of care is the gastrectomy.

## ENDOSCOPIC TREATMENT

Endoscopic treatment (ER): EMR as well as ESD of early carcinomas is only meaningful if lymph node metastasis can be excluded. This is not possible by endoscopic ultrasonography or computed tomography because the size of the lymph nodes (LN) is not a reliable parameter for detection of metastatic infiltration. This has been shown for early as well as advanced gastric cancer<sup>[24,25]</sup>. Therefore, the indication for endoscopic treatment is an on-going debate between surgeons and gastroenterologists.

EMR: Since endoscopic mucosal resection using the strip biopsy method (two-channel method) was first introduced for endoscopic therapy in 1984<sup>[26]</sup>, various methods of EMR have been developed, including endoscopic resection with a cap-fitted panendoscope (EMRC). They are widely used in Western countries as well as Japan<sup>[8,27]</sup>. Lesions with an extremely low likelihood of lymph node metastasis have been identified by clinicopathological investigations of multiple surgery cases, and indications for endoscopic therapy have been compiled by the Japan Gastric Cancer Association<sup>[2]</sup>. In principle, these indications state that the likelihood of lymph node metastasis is extremely unlikely and that the tumor should be of a size and in a site that allows it to undergo en bloc resection. Specifically, the lesion must be (1) a differentiated elevated intramucosal cancer less than 2 cm in size or (2) a differentiated depressed intramucosal cancer less than 1 cm in size without ulcer findings. However, due to the nature of the excision

technique, which uses a snare, EMR also has the disadvantage that only a small area can be excised at a time, and so for larger lesions, it has higher rates of piecemeal excision and local recurrence<sup>[8]</sup>. Manner *et al*<sup>[28]</sup> summarized the Western results of EMR as follows: Although ER for EGC in Western countries is effective; it is associated with a relevant risk of complications. In view of the possibility of recurrent or metachronous neoplasia, a strict FU protocol is mandatory.

Endoscopic submucosal dissection is a new technique that can remove even large tumours in one piece<sup>[29]</sup>. In a comparison with endoscopic mucosal resection, resections removing tumours in one piece were more frequent in the endoscopic submucosal dissection group (93% *vs* 56%) and the 3-year recurrence-free rate was higher (98% *vs* 93%), at the expense of a higher rate of perforations (3.6% *vs* 1.2%), which were endoscopically managed in most cases<sup>[30]</sup>. Several reports from Western referral centers could confirm the high rates of en bloc resection of early gastric neoplasia. However, histology may not always confirm complete resections of horizontal tumor margins<sup>[31-33]</sup>.

Regarding the German S3 guideline for gastric cancer the endoscopic treatment is provided for non ulcerated lesion smaller than 2 cm showing an intestinal type according to the Laurén classification. For bigger lesions and small diffuse carcinomas an endoscopic treatment can be considered<sup>[34]</sup>.

## SURGICAL TREATMENT

The surgical resection of the tumor is the only possibility to cure a patient with early gastric cancer and lymph node metastasis. The age-adjusted survival rates for these patients are comparable with the normal population<sup>[35]</sup>. The presence of lymph node metastasis is one of the most important prognostic factors in patients with gastric carcinoma. Node-negative patients have a better outcome, nevertheless a subgroup of them experience disease recurrence. Baiocchi *et al*<sup>[36]</sup> analyzed the clinicopathological characteristics of lymph node-negative advanced gastric carcinoma patients submitted to gastrectomy and D2 lymphadenectomy with a retrieved number

of nodes greater than 15, after an actual follow-up of almost 5 years, and evaluate outcome indicators. Data of 301 patients with curative gastrectomy staged as N0 between 1992 and 2002 of 7 centers participating to the Italian Research Group for Gastric Cancer were included. Disease-specific and disease-free survival after 3, 5, and 10 years were 90.4%, 86.1%, 75.9%, and 72.1%, 57.3%, 57.3%, respectively. Mortality was 1.7%. The factors associated with a better disease-free survival at univariate analysis were age < 60, T2 tumors, distal location, intestinal histotype, and number of retrieved nodes > 25; depth of infiltration and histotype were the only 2 independent predictors of 5-year recurrence-free survival at multivariate analysis.

Therefore, the German national guidelines for gastric cancer suggests that only mucosal cancer without LNM can be treated endoscopically if a R0-resection is possible<sup>[34]</sup>.

The guidelines do not dictate the indication for a subtotal gastrectomy, however a D2 lymphadenectomy and a resection margin of 5 cm for intestinal type and 8 cm for diffuse type of gastric cancer is provided. As Hosokawa *et al*<sup>[37]</sup> show a subtotal gastrectomy to be equal to total gastrectomy concerning the outcome of early remnant gastric cancer patients who underwent endoscopic treatment at first; there is evidence for the efficiency of the limited surgical treatment. But so far, there is a lack of data regarding this approach in early gastric cancer in western countries.

## LYMPHADENECTOMY

For many years, clinicians have debated whether an extended lymph-node dissection (D2) for gastric cancer is beneficial. So far, five randomised studies comparing D1 and D2 dissections have been completed. A Cochrane review showed a significantly increased mortality after D2 dissection (RR = 2.23, 95%CI: 1.45-3.45), without a benefit in survival; HR = 0.95, 95%CI: 0.83-1.09<sup>[38]</sup>.

A single-centre randomised trial comparing D1 and D3 dissections was the first to identify a difference ( $P = 0.041$ ) between overall survival in D1 dissections (53.6%, 95%CI: 44.2-63.0) and D3 dissections (59.5%, 95%CI: 50.3-68.7). No postoperative deaths occurred and morbidity was 12%. Only 13% of patients in this study had pancreatico-splenectomy compared with 23% in the Dutch gastric cancer trial<sup>[39]</sup>. Analysis of the group that did not undergo a pancreatico-splenectomy in the Dutch trial showed a significant survival advantage for those who had a D2 lymph-node. Thus, a D2 dissection might be beneficial if postoperative mortality can be avoided. Strong *et al*<sup>[40]</sup> compared pT1 pN0 gastric cancer from United States with those from Korea. They could show that if patients had a D2-lymphadenectomy the prognosis was comparable for both groups of patients. Instead of these results the guidelines for the extension of lymphadenectomy for early cancer is different between

Europe and United States. National guidelines from the Netherlands or from Germany recommended a D2-LAD for resectable gastric cancer<sup>[34]</sup>. The actual version of The NCCN Clinical Practice Guidelines in Oncology for Gastric Cancer recommended for patients with resectable locoregional cancer, a gastrectomy with a D1+ or a modified D2 lymph node dissection (performed by experienced surgeons in high-volume centers). Postoperative chemoradiation is the preferred option after complete gastric resection for patients with node-positive T1-T2 tumors. Postoperative chemotherapy is included as an option after a limited lymph node dissection for this group of patients<sup>[41]</sup>.

## PREDICTION OF LYMPH NODE METASTASES

The key issue for the decision of endoscopic or surgical treatment is the existence of lymph node metastasis. For rational LN dissection it is important to know the incidence of metastasis at each LN station. For this purpose a computer program was developed using data from 4302 primary gastric cancers treated at the National Cancer Center Hospital in Tokyo between 1969 and 1989<sup>[42]</sup>. The accuracy of this program for European patients was evaluated by several authors<sup>[43-46]</sup>. The Maruyama computer program showed good predictive ability for LN metastases in most of the 16 LN stations. The predictive values could be improved using a neural network for the prediction of LN's<sup>[44,45]</sup>.

The probability of lymph node metastasis is a key criterion for defining subgroups of patients for whom these endoscopic methods are appropriate. The main focus of the current discussion is m3 and sm1. Hölscher *et al*<sup>[10]</sup> described an algorithm for a group of patients with early cancer in Germany using only variables which are available before therapeutic decision. Using this clinical pathway all carcinomas with lymph node metastasis and 50% of those without LNM were correctly predicted.

A more invasive method is the Sentinel lymph node (SN) biopsy. The technique is based on the concept that the tumor-bearing status of the SN, which is defined as a LN that directly drains a specific cancer, reflects the tumor status of the remaining nodes. In a Japanese multicenter trial the feasibility and accuracy of diagnosis using SN biopsy in T1 gastric cancer was evaluated. The proportion of false negatives was much higher than expected. And the authors conclude that intraoperative histological examination using only one plane is not an appropriate method for clinical application of SN biopsy in gastric cancer surgery<sup>[47]</sup>.

## MINIMAL-INVASIVE SURGERY

Since the first report of laparoscopic gastrectomy in 1994 by Kitano *et al*<sup>[48]</sup> in Japan, much of our knowledge on the feasibility, safety, and benefits of laparoscopy in the treatment of gastric cancer is derived from studies performed



in the East. Data from the West have emerged at a slower pace. This is largely because the disease incidence is much lower and a greater proportion of patients present with locally advanced tumors that render laparoscopic resection less feasible. In addition, up to 50% of gastrectomies for adenocarcinoma in the US are performed at low volume centers where experience with advanced laparoscopic gastric surgery is limited. As a result, conventional open gastrectomy is still performed much more frequently in the US than laparoscopic resection even for patients with early stage disease<sup>[6]</sup>. Corcione performed during a time span of 12 years laparoscopic gastrectomy with D2-lymphadenectomy in 11 patients with early gastric cancer. The five year survival rate was 100%<sup>[49]</sup>. In Japan, early stage gastric cancer (T1N0 or T2N0) is regarded as the only indication for laparoscopic gastrectomy. Cancer registry data from United States as well as from the Netherlands showed that more than 90% of the patients with stage I gastric cancer were surgically resected<sup>[50]</sup>.

## CONCLUSION

Physicians from Western countries had much learned about treatment of gastric cancer from the great experience of their Eastern colleagues. Patients with adequate treated early gastric cancer have the same prognosis as normal population. Therefore the main goal of future research is to reduce the side effects of the therapy and to improve the quality of life after therapy. Actual topic of cancer research is personalized therapy. One example may be the ToGA-trial (Trastuzumab for Gastric Cancer), the first international trial to include patients with human epidermal growth factor 2 (HER-2) positive advanced/metastatic gastric or gastroesophageal junction cancer. For patients with HER-2 positive advanced gastric cancer Trastuzumab, an anti-HER2 monoclonal antibody, survival benefit was shown and becomes the first targeted agent approved in these tumors<sup>[51]</sup>. But only 20% or less of all patients are HER-2 positive. To date, monoclonal antibody therapy is the only immunotherapy approved by the United States Food and Drug Administration for gastrointestinal cancers. Initial trials validating new immunotherapeutic approaches, including vaccination-based and adoptive cell therapy strategies, for gastrointestinal malignancies have demonstrated safety and the induction of antitumor immune responses. Therefore, immunotherapy is at the forefront of neoadjuvant as well as adjuvant therapies for the treatment and eradication of gastric cancer<sup>[52,53]</sup>.

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