

## Early Gastric Cancer: An Overview and Future Perspective

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### Abstract

Early gastric cancer is a gastric cancer limited to the mucosa, sub mucosa, or both, regardless of lymph node status and offers an excellent (over 90%) chance of cure based on surgical resection. In this review the Author provide an overview on epidemiology, diagnosis and management of EGC, both in Western and Eastern series, with special concern to prognostic factors and long term follow up.

**Keywords:** Early gastric cancer; Adenocarcinoma; Gastroenterological endoscopy

### Introduction

Early gastric cancer (EGC) is an adenocarcinoma confined to the mucosa or sub mucosa irrespective of lymph node involvement. The term "early" is related to primary lesion features and not to "early" detection. This histological entity, as defined in 1962 by the Japanese Society of Gastroenterological Endoscopy, was based on the observation that gastric cancer of this type had a favorable prognosis, with a five year survival greater than 90% [1,2].

### Prevalence

According to the world estimate of cancer incidence in the year 2008 by the International Agency for Research on Cancer [3], gastric cancer is still one of the most common cancers in the world. About one million new cases of stomach cancer were estimated to have occurred in 2008 (988 000 cases, 7.8% of total number of cancers), making it currently the fourth most common malignancy in the world, behind cancers of the lung, breast and colon/rectum. More than 70% of cases (713 000 cases) occur in developing countries, and half the world total occurs in Eastern Asia (mainly in China and Japan), whereas 165 000 new cases occur in WHO-Europe Region (16.7 %) and 21 000 cases (2.1 %) in USA. The highest mortality rates are estimated in Eastern Asia (28.1 per 100,000 in men, 13.0 per 100,000 in women), the lowest in Northern America (2.8 and 1.5 respectively). Wide screening campaigns are extensively performed on general population in areas with high prevalence of gastric cancer; this screening policy has allowed the detection of high rates of early gastric cancer with positive impact on prognosis and mortality rates [4]: in Japan, the rate of EGC has increased from 15% a few decades ago to 50% of all endoscopically diagnosed gastric cancers at present. The clinicopathological features of this disease and their prognostic relevance have been extensively analyzed in several studies based upon very large series, often over 1000 cases [5,6]. On the other hand, in low prevalence areas, such as in Europe or in USA, screening campaigns are not feasible and advanced gastric cancer is the most common diagnosis; therefore treatments have little chance to affect prognosis and mortality [7]. In the West, the frequency of EGC has only increased from 10% to about 15 or 20% [8] and large numbers of cases usually are not achieved, even if Everett and Axon concluded, in a large review, that clinicopathological features in Japan and in Western countries are quite similar [7].

### Diagnosis

More patients with EGC are diagnosed today, and new techniques have resulted in better quality of life for these patients. It is now widely accepted that early gastric cancer is a different disease with high survival rates after accurate resection; about 95% of patients survive at 5 years, as reported both from Western and Japanese surgeons [9].

The most widely used classification of EGC [10] is based upon the macroscopic appearance of the tumor. EGC is divided into tumors that are protruded (I), superficial (II), and excavated (III). Type II is further subdivided into elevated (IIa), flat (IIb), and depressed (IIc). Type IIc is the most frequent lesion whereas there is a low percentage of a type III lesion (less than 1%). Superficial tumors with two or more components account for the 20% of the cases.

A helpful pathological classification for gastric cancer was described by Lauren in 1965 [11]. Tumors are divided into those with gland formation (intestinal type) and those without glandular characteristics (diffuse type). Intestinal type occurs more commonly in older patients in areas with a high incidence of gastric cancer, whereas diffuse type has a constant rate worldwide and occurs in a younger age group. This classification is in widespread use in the West; a large systematic review has reported that in EGC, intestinal type predominates, accounting for more than half of the patients in 16 out of 18 studies and more than 70% in seven of the eighteen [7].

Endoscopy with biopsy is the gold standard in achieving the diagnosis of early gastric cancer. This technique requires a remarkable ability and experience of the endoscopist in order to identify the lesion, that often shows minimal alterations compared with the surrounding healthy mucosa.

In Japan, endoscopists are able to distinguish early gastric cancers from advanced gastric lesions in over 84% of patients that are submitted to gastroscopy [12]. It is a matter of fact that in Europe the most part of gastric cancers are diagnosed at stage IV, probably because Western endoscopists have limited experience of this cancer due to its less incidence rates in Europe and in North America. Furthermore, in Asia, chromoendoscopy (that is able to detect intestinal metaplasia, dysplasia or early gastric cancer) has been introduced as standard technique since '80s, whereas in Western countries these methods became established in late 90s only [13,14].

The capability to detect early gastric cancer lesions has been further enhanced by means of magnifying gastroscopy that is useful in differentiating between benign and malignant gastric mucosal lesions. Furthermore, recent studies have proved the usefulness

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Received May 10, 2013; Accepted June 11, 2013; Published June 13, 2013

**Citation:** Iascone C, Vallerani D (2013) Early Gastric Cancer: An Overview and Future Perspective. J Gastroint Dig Syst S12: 013. doi:10.4172/2161-069X.S12-013

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of magnifying endoscopy with narrow-band imaging (M-NBI) in the diagnosis of superficial (non-polypoid) elevated lesions of the stomach [15].

Multivariate analyses have demonstrated that main prognostic factors in patients with EGC are related to tumor characteristics and patient features, whereas the type of surgical intervention does not affect long-term survival. Age, tumor extended to submucosa, lymph node invasion are independent prognostic factors. Five-year survival ranges from 57% for patients with lymph node metastases to more than 90% when metastatic spread at lymph nodes is absent, with lesions occurring especially in the antrum and pyloric region of the stomach [16-19].

Haematogenous metastases at the time of diagnosis from early gastric cancer are extremely rare, because tumor is completely limited to the gastric wall, so only lymph node metastases are observed in the clinical practice.

Recent studies confirm that neoplasms confined to mucosa seldom spread to lymph nodes (about 4%), whereas early gastric cancers with submucosal invasion show lymph nodes metastases in 20% of patients, far from the 50% of lymph node involvement in patients with T2 lesions [20]. These data are based on a single lymph node section evaluation and could underrate the real lymph node involvement; other studies, based on multiple sections, demonstrate that lymph nodes could be involved in a higher percentage (more than 20% in comparison to single sections) [21]. In order to assess causes of recurrence in patients with EGC, more studies have been conducted in patients with R0 resections and N0, evaluating negative nodes by IHC (anti-cytokeratin antibodies). The results suggest that worse prognosis in N0 patients are probably due to microscopic metastases detected with IHC [22].

Larger tumor sizes correlate with a worse prognosis, because a close relationship has been demonstrated between size and depth of gastric wall invasion and N1 metastases (perigastric lymph nodes). Furthermore, if tumor size exceeds 20 mm, N2 metastases are detected in 5% of patients. In these latter cases, there is wide consensus on D2 lymphadenectomy as the appropriate curative resection [23,24].

## Management

Current strategies in the management of early gastric cancer show remarkable differences between Japan and Western countries. In general, the most widely and successfully performed operation for EGC is gastrectomy (distal, proximal or total) with D2 lymphadenectomy. This procedure has been performed routinely in Japan, but has gained increasing acceptance in Europe only in recent years. Nevertheless, while European surgeons have been gradually adopting more extended resections, the Japanese surgeons have simultaneously shifted to more conservative surgery. Endoscopic mucosal resection (EMR) was introduced in 1978 and later endoscopic submucosal dissection (ESD) has been also successfully implemented [25,26], in addition to modified gastric resections.

EMR is indicated for patients with EGC at stage IA (T1N0), fulfilling criteria as follows: tumor confined to mucosa, type I or IIA (protruded or superficial elevated) or type IIC (superficial depressed), well or moderately differentiated, with the largest diameter being less than 20 mm [27,28]. Stage IB (T1N1) should be treated with total or modified gastric resection, whereas stage II tumors require standard gastrectomy independently from other parameters [27,28]. Nevertheless, even if in Japan high percentages (more than 20%) of EGCs are treated with EMR or ESD, total or subtotal gastrectomy with D2 lymph nodes dissection still seems to be widely recommended. These leanings are supported by

two observations: first, D2 lymph nodes are occasionally involved when tumor is extended to submucosa; second, as aforesaid, tumors routinely classified as N0 could be understaged as micrometastases could be detected at IHC up to 50% of cases [21,22].

As IHC method is not feasible in common practice, clinical research has been focused on lymph node status as prognostic factor, evaluated with standard histology: the main question concerns the number of lymph nodes dissected that is requested for a correct staging in order to achieve surgical radicality with less extended lymphadenectomies than D2 dissections [29-31].

Among Far Eastern Authors, Ichikura [32], has suggested at least 10 lymph nodes to be dissected to classify patients as N0, and even 20-30 lymph nodes for a correct N1 N2 staging. On the other hand, in 2006, a study conducted in Italy by the GIRCG (Gruppo Italiano Ricerca sul Cancro Gastrico, Italian Research Group in Gastric Cancer) on 652 EGCs [29] reported that even only 3 metastatic lymph nodes account for a poorer prognosis, with 5-year survival rate ranging from 92% (patients N0) to 82% (patients with 3 or less positive lymph nodes). Furthermore, in the Italian series, increased recurrences are observed in patients with less than 15 dissected lymph nodes, although negative for metastases (N0). This finding confirms that at least 15 lymph nodes dissected are requested to achieve a correct tumor staging. Unfortunately, the lymph node factor hasn't been extensively investigated at present with a multivariate analysis [19,33,34]. The number of metastatic lymph nodes depends on the number of dissected lymph nodes, which, in turn, is based on diagnostic procedures and type of surgical intervention [35,36]. These remarks are indeed a strong background for recent discussion on the TNM classification of gastric cancer, with special regard to the N parameter. TNM provides a simple and reproducible staging but at least 15 lymph nodes dissected are required and, if this number is not achieved, "understaging" of N parameter may occur ('stage migration'). Therefore in the Eastern countries D2 dissection is currently performed with very low recurrence rates. European surgeons have tried to emulate the Japanese results and Dutch1 and UK2 trials [37,38] have examined whether extended lymphadenectomy might prove as effective in Western patients. D1 dissection and more radical D2 dissection showed little difference in terms of survival in both trials; furthermore, a Cochrane review has concluded that extended lymphadenectomy provides no benefit versus limited lymphadenectomy [39]. Although further trials might determine the best procedure for Western patients, treatment decisions are now being made on the basis of surgical opinion and so Western surgeons routinely perform D1 dissection.

In order to better define the N parameter, the number of positive lymph nodes should be evaluated in connection with the number of dissected lymph nodes [36].

A recent study conducted in our Department has demonstrated that both lymph node metastases and lymph node "ratio" are independent prognostic factors at the multivariate analysis and this finding suggests promising therapeutic strategies (Iacone et al., unpublished data). Our results, according to other Italian Authors [30], support the choice of performing D1 dissection as it allows a correct staging if N "ratio" is evaluated, bypassing the unresolved D1-D2 lymphadenectomy choice. Furthermore, in early diseases, as in our series, the long term survival is not negatively affected by limited lymphadenectomies.

## Prognosis/outcomes

Early gastric cancer (EGC) has a very favorable prognosis: in a report from the National Cancer Center of Tokyo concerning 1475

patients with EGC, only 1.4% was found to have recurrent disease and a similarly low rate was reported from 1452 patients with EGC from Korea [40].

The time scale over which disease recurs is a matter of discussion. Regarding recurrence times, Lee et al. [41] reported that the majority (62%) of recurrences is detected at less than 2 years and fewer than 10% occurred after 5 years. On the other hand, Sano et al. [42] reported that 23% of deaths from recurrences occurred after 5 years and 40% within the 3 years.

In our series overall survival and rate of recurrences are very favorable: 5-year overall survival = 94.5%, deaths for recurrence = 34.8% of total number of deaths after a 20-years survey, confirming the good prognosis of EGC. However, it is to emphasize that the few cases of recurrence deaths occurred in patients with a follow-up longer than 15 years (up to 20 years), suggesting that patients with EGC should be monitored for longer periods than patients with advanced gastric cancer, because they should not be considered fully recovered after 5-10 years of surveillance.

## Conclusions

Early gastric cancer is a tumor with a very good prognosis, with high survival rates in comparison with advanced gastric cancer and there is wide consensus on lymph nodes invasion as main independent prognostic factor. However, mortality among these patients' remains a concern and long-term follow up seems to be necessary even for patients successfully treated for EGC, as suggested from recent studies.

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This article was originally published in a special issue, [Gastrointestinal Cancer](#) handled by Editor(s). Dr. Aliasger Amin, James Cook University Hospital Middlesbrough, United Kingdom