Natural history of early gastric cancer: series of 21 cases

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ABSTRACT

Background and study aims While knowledge of the natural history of early gastric cancer (EGC) may be useful in relevant clinical situations, few relevant reports are available. Therefore, we investigated the progression of EGC. We gathered data regarding 114 cases of EGC from 2005 to 2015 from a hospital cancer registry and analyzed 21 lesions that fulfilled five inclusion criteria. Deep progression was defined as submucosal invasion by a mucosal tumor and proper muscle invasion by a submucosal tumor. Lateral progression was defined as ≥20 % increase in size. During median follow-up of 23 months, one of 18 mucosal tumors showed deep progression and six showed lateral progression. Of three submucosal tumors, two showed deep progression and three showed lateral progression. Our study suggests that a certain proportion of mucosal cancers can lie dormant for several years. Further large-scale studies in a multicenter setting should overcome the limitations of this study.

Introduction

Early gastric cancer (EGC) carries a definite risk of progression and affects survival [1, 2]. However, we sometimes experience a subset of gastric cancer (GC) which progresses very slowly. Information regarding the natural history of EGC may be useful in various clinical situations because older patients, those with limited life expectancy, or those at high operative risk should be informed about the expected outcomes for non-operative management of GC.

Non-operative management is divided into endoscopic treatment, no treatment with follow-up, and no follow-up. Even if curing the lesion is difficult, endoscopic treatment may be performed at the patient's request because tumor reduction may delay appearance of symptoms and relieve pain. No follow-up is chosen when EGC is considered not to be a prognostic factor for reasons such as other cancers or diseases. No treatment with follow-up is selected when endoscopic treatment is not performed for reasons such as the patient's advanced age or poor general condition. In this case, the natural history of EGC
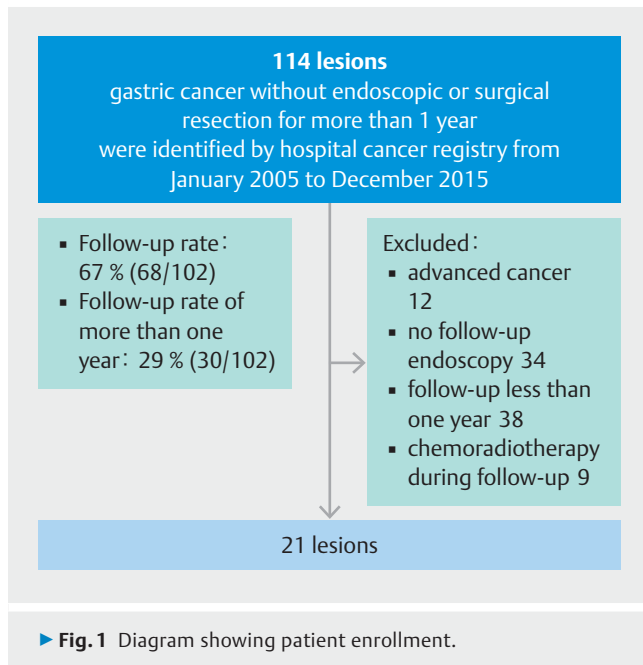
helps treatment decision-making. However, there have been few reports on the natural history of EGC, especially regarding early-stage cancer.

Therefore, we aimed to investigate progression of EGC in Japan, mainly mucosal cancer (i. e., mucosal high-grade neoplasia [HGN] in Western countries) and to clarify the natural history of EGC based on endoscopic follow-up data.

Case reports

This was a retrospective study conducted at the Osaka International Cancer Institute. Patient inclusion criteria were as follows: (1) endoscopically diagnosed mucosal or submucosal lesion; (2) histologically diagnosed adenocarcinoma on biopsy specimen; (3) no surgical or endoscopic resection for more than 1 year; (4) no exposure to chemotherapy or radiation for GC or other primary cancers; and (5) one or more endoscopic follow-ups.

Follow-up endoscopic examinations were conducted mainly to monitor progression of cancer. Depth of tumor invasion was

Iwagami Hiroyoshi et al. Natural history of… Endoscopy International Open 2019; 07: E43–E48

E43

114 lesions
gastric cancer without endoscopic or surgical resection for more than 1 year were identified by hospital cancer registry from January 2005 to December 2015

- Follow-up rate: 67 % (68/102)
- Follow-up rate of more than one year: 29 % (30/102)

Excluded:
- advanced cancer 12
- no follow-up endoscopy 34
- follow-up less than one year 38
- chemoradiotherapy during follow-up 9

21 lesions

▶ **Fig. 1** Diagram showing patient enrollment.

determined by endoscopic findings, such as thickness of the lesion, stiff protrusion, marginal elevation, remarkable redness, and irregularity of the surface [3,4]. Deep progression (DP) was defined as submucosal invasion by a mucosal tumor and proper muscle invasion by a submucosal tumor. Lateral progression (LP) was defined as ≥20 % increase in size. The size of lesions was estimated by comparison with the known diameter of an endoscope or open forceps.

Vital status and causes of death were confirmed by medical charts. Patients who died from causes other than GC were regarded as censored at the time of death. Patients with unknown vital status were also treated as censored at the time when they were last known to be alive. Time to progression was measured from date of diagnosis to first date of deep progression or lateral progression. The time-to-progression curve was generated using the Kaplan-Meier method. Statistical analysis was carried out by R version 3.3.3 (http://www.r-project.org).

Twenty-one lesions fulfilled all the inclusion criteria (▶ **Fig. 1**). A summary of characteristics of the patients and lesions is shown in ▶ **Table 1**. The follow-up rate was 67 % (68/102) and that for more than 1 year was 29 % (30/102). The reasons for no treatment with follow-up were an obfuscated lesion in five patients, refusal of the patient in six cases, other primary advanced cancers in eight, and other serious disease in two patients. Among 34 patients with no treatment and no follow-up, the reasons were other primary advanced cancer in seven, poor nutrition in one, and unknown in 26 patients. Results of an endoscopic examination and progression are shown in ▶ **Table 2**. Median follow-up periods for intramucosal and submucosal cancers were 26.5 and 16 months, respectively. Of 18 mucosal tumors, one showed DP and six showed LP. Of three submucosal tumors, two showed DP and three showed LP.

Clinical course of two progressive cases
Patient 5
The lesion was estimated to be submucosal cancer because of SMT (submucosal tumor)-like marginal elevation (▶ **Fig. 2a**). Twelve months later, it was up to 100 mm and the depression progressed more deeply (▶ **Fig. 2b**). Sixteen months later, the elevation became more obvious. The lesion was finally estimated to be cancer invading into the muscularis propria or deeper (▶ **Fig. 2c**).

Patient 21
The lesion was estimated to be submucosal cancer (▶ **Fig. 3a**) by the thickness and marginal elevation. Twelve months later, it was up to 50 mm and estimated to be muscularis propria cancer because the thickness and elevation became more obvious (▶ **Fig. 3b**).

Clinical course of a dormant case
Patient 11
The lesion was initially diagnosed as intramucosal cancer, (▶ **Fig. 4a**) and the diagnosis has remained mucosal cancer for 110 months (▶ **Fig. 4b**).

Discussion

In our case series, only one of 18 mucosal tumors showed DP and six showed LP. Of three submucosal tumors, two showed DP and three showed LP.

Several studies have investigated the natural history of noninvasive gastric neoplasia based on histological follow-up data in a Western population. A report from Italy showed that 17 % of noninvasive neoplasias had evolved to invasive GC during an average follow-up of 52 months [5]. A study from the Netherlands reported an annual incidence of invasive GC of 0.6 % for mild-to-moderate dysplasia and 6 % for severe dysplasia [6]. These data provide important information because intramucosal invasive cancer of the stomach, unlike intramucosal carcinoma of the colon, metastasizes. However, the distinction between intramucosal invasive cancer and HGN or carcinoma in situ can be challenging when evaluated by histological examination of the mucosal surface. Considering that these studies were based on biopsy specimens taken from the surface of mucosa, the reliability of differential diagnosis of invasive or noninvasive neoplasm is limited.

In another study, progression of EGC was investigated based on endoscopic follow-up data in a Japanese population [7]. This report from Osaka showed a cumulative 5-year risk of progression to the advanced stage of 63.0 % in 71 patients. However, in this study, initial depth of tumor invasion was not differentiated into mucosal and submucosal cancer. Because mucosal cancer in Japan includes noninvasive neoplasia, risk of progression to advanced cancer may differ substantially between mucosal and submucosal cancer. In the current study, only one of 18 mucosal cancers (mucosal HGN in Western countries) showed DP and six showed LP. These results suggest that a certain proportion of mucosal tumors can lie dormant for several years.

E44

Iwagami Hiroyoshi et al. Natural history of … Endoscopy International Open 2019; 07: E43–E48

▶ **Table 1** Summary of 21 EGC cases.

| Case	Sex	Age	Reasons for no treatment	Endoscopic follow-up period (month)	Number of endoscopic examinations	Initial findings					LP or not	DP or not	Outcome	Depth of invasion in the resected specimens
						Location	Morphological type	Depth of invasion	Size (mm)	Histological type				
1	M	79	Once obfuscated	32	7	M	IIa	M	6	Tub1	Yes	No	ESD	M
2	M	93	With other cancer	27	4	U	IIa	M	8	Tub1	No	No	Unknown	
3	M	71	With other cancer	13	2	L	IIc	M	15	Sig	Yes	No	Death from esophageal cancer	
4	M	85	Obfuscated	26	3	U	IIc	M	4	Tub2	No	No	Alive without treatment for EGC	
5	M	76	With other cancer	16	2	M	IIc	SM	50	Tub2	Yes	Yes	Unknown	
6	F	63	With other cancer	17	3	L	IIc	M	5	Por	No	No	Death from gynecologic cancer	
7	M	72	Obfuscated	38	6	L	IIc	M	5	Tub1	No	No	Alive without treatment for EGC	
8	M	76	No wish for treatment	14	1	L	IIc	M	6	Tub1	Yes	No	Alive without treatment for EGC	
9	M	86	Obfuscated	19	3	L	IIc	M	8	Tub1	No	No	Alive without treatment for EGC	
10	M	72	With other cancer	16	3	L	IIa	M	10	Tub1	Yes	Yes	Death from esophageal cancer	
11	M	67	No wish for treatment	110	9	L	IIa	M	10	Tub1	No	No	Alive without treatment for EGC	
12	M	59	With other disease	16	3	L	IIc	SM	30	Tub1	Yes	No	ESD for EGC, but death from HCC	M

▲ Table 1 (Continuation)

| Case	Sex	Age	Reasons for no treatment	Endoscopic follow-up period (month)	Number of endoscopic examinations	Initial findings			Size (mm)	Histological type	LP or not	DP or not	Outcome	Depth of invasion in the resected specimens
						Location	Morphological type	Depth of invasion						
13	M	73	With other cancer	41	6	L	IIa	M	8	Tub1	Yes	No	Alive without treatment for EGC	
14	M	77	No wish for treatment	52	5	L	IIa	M	6	Tub1	No	No	ESD	M
15	M	48	With other cancer	37	3	L	IIc	M	20	Sig	No	No	Death from lung cancer	
16	F	90	No wish for treatment	21	4	L	IIc	M	15	Tub1	No	No	Unknown	
17	F	78	No wish for treatment	41	4	L	IIc	M	10	Tub1	No	No	ESD	M
18	M	71	Obfuscated	31	3	L	IIa	M	4	Tub1	No	No	Alive without treatment for EGC	
19	M	55	With other disease	17	1	L	IIc	M	8	Tub1	Yes	No	ESD	M
20	M	79	No wish for treatment	23	2	L	IIa	M	3	Tub1	No	No	Alive without treatment for EGC	
21	M	80	With other cancer	18	3	L	IIc	SM	30	Tub2	Yes	Yes	Unknown	

EGC, early gastric cancer; LP, lateral progression; DP, deep progression; M, middle thirds of stomach; U, upper thirds of stomach; L, lower thirds of stomach; IIa, superficial elevated type; IIc, superficial depressed type; M, intra-mucosal cancer; SM, submucosal cancer; Tub1, well differentiated tubular adenocarcinoma; Tub2, moderately differentiated tubular adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet ring cell carcinoma; HCC, hepatocellular carcinoma

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▶ **Table 2** Results of endoscopic examination and progression.

		n = 21
Endoscopic follow-up period, median (range), months		23 (13 – 110)
Number of endoscopic examinations, median (range)		3 (1 – 9)
	Mucosal cancers (n = 18)	Submucosal cancers (n = 3)
Lateral progression, n(%)	6 (33)	3 (100)
Deep progression, n(%)	1 (6)	2 (67)
Median degree of lateral progression	50 %	67 %
Cumulative 1- and 3-year risk for lateral progression	6 % and 31 %	Both 100 %
Cumulative 1- and 3-year risk for deep progression	0 % and 6 %	33 % and 100 %
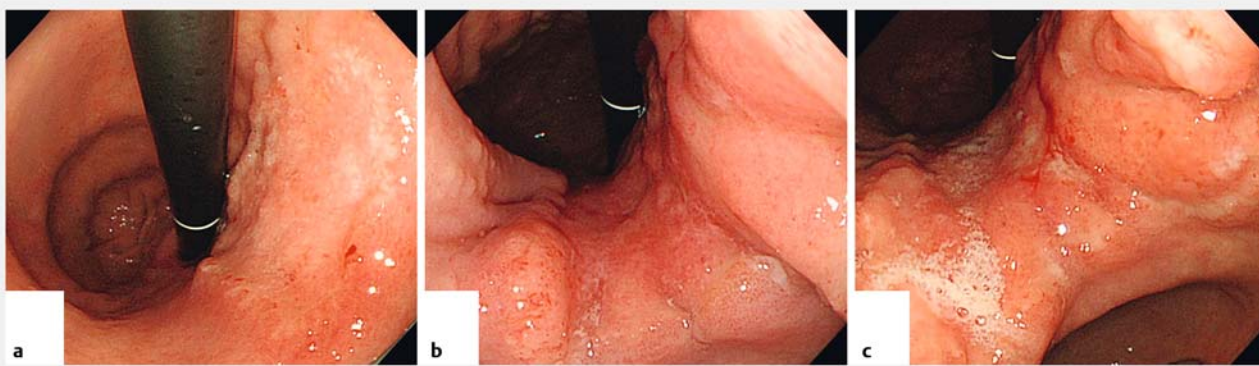
▶ **Fig. 2** Case 5: Lesion with lateral progression and deep progression (submucosal cancer to advanced cancer).
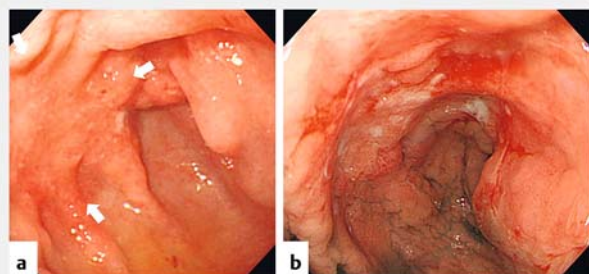
▶ **Fig. 3** Case 21: Lesion with lateral progression and deep progression (submucosal cancer to advanced cancer).

▶ **Fig. 4** Case 11: The lesion was initially diagnosed as intramucosal cancer, and the diagnosis has remained mucosal cancer for 110 months.

When we consider the implications of DP and LP, DP is equivalent to advancement of the T category (i. e., T1a to T1b or T1b to T2). The T category is a main component of TNM staging and is associated with GC prognosis [8, 9]. However, LP is not a component of TNM staging, and the relationship with prognosis remains unclear. However, lesion size is a significant predictive factor for metastasis [8] and may indirectly be associated with prognosis. Based on these findings, DP and LP are considered in oncological terms as worsening.

The inclusion process for patients without treatment may be biased by some factors. A detailed database would help to identify all patients who fulfill the study criteria. Most hospitals may have a database of patients who have received treatment, but no such register for those not undergoing treatment. Another data source may then be used to identify the patients without treatment, such as medical charts or endoscopic records. However, untreated patients with short follow-up would be missed because they may have fewer follow-up visits or examinations.

Iwagami Hiroyoshi et al. Natural history of … Endoscopy International Open 2019; 07: E43–E48

E47

To overcome these shortcomings, we used the cancer registry to identify untreated patients with GC. This registry integrates histology, treatment, drug, and accounting databases, and includes dates of diagnosis and treatment. By combining multiple databases, the cancer registry can accumulate more patients than a single database and thus minimize the risk of overlooking patients with cancer. By referral to dates of diagnosis and treatment in the cancer registry, patients with no treatment or delayed treatment can be identified.

There are some limitations to the current study. The first limitation is the small number of patients. GC comprises a heterogeneous group of diseases with various histological types (differentiated or undifferentiated) and morphological types (elevated or depressed). Risk of progression may differ among these forms. However, the potential predictive factors for progression were not identified in our study because of the limited number of progressive cancers. A median follow-up of 23 months might be insufficient to clarify the natural history of GC, especially in revealing whether this type of cancer progresses to eventual death.

Another limitation is the low follow-up rate of 67 % in this study. The follow-up rate, a standard index of completeness, is important for assessing the validity of a cohort study [10]. However, we consider the follow-up rate in this study was low because most patients with no treatment returned to previous doctors. The other limitation is that the judgement of DP, particularly for progression from submucosal cancer to proper muscle invasion, is difficult and can be subjective.

Conclusion

In conclusion, our study suggests that a certain proportion of mucosal cancers can lie dormant for several years. Further large-scale studies in a multicenter setting should help to overcome the limitations of this study.

Competing interests

None

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E48

Iwagami Hiroyoshi et al. Natural history of … Endoscopy International Open 2019; 07: E43–E48