Natural history of early gastric cancer: a non-concurrent, long term, follow up study

H Tsukuma, A Oshima, H Narahara, T Morii

Abstract

Background—Controversy has arisen on the natural history of early gastric cancer (EGC). While some emphasise the effectiveness of early detection in reducing mortality from gastric cancer, others insist that EGC is a pseudo-cancer.

Aims/patients/methods—To elucidate the natural history of EGC, a non-concurrent, long term, follow up study was conducted in 71 patients who were diagnosed endoscopically as having EGC, which was confirmed as cancer on biopsy, but in whom surgical resection was not conducted or delayed by more than six months.

Results—The natural course of EGC was observed in 56 cases. Over a period of 6–137 months, 20 remained in the early stage while 36 progressed to the advanced stage. The proportion remaining in the early stage consistently decreased with time. Median duration of those who remained in the early stage was estimated as 44 months. The cumulative five year risk for progressing to the advanced stage was 63.0%. In 38 cases there was no evidence for undergoing surgical resection for gastric cancer. The cumulative five year corrected survival was estimated as 62.8% among those unresected. Hazard rate ratio for gastric cancer mortality was 0.65 (p=0.34) for screening detected versus non-screening detected. Hazard rate ratio for gastric cancer mortality was 0.51, significantly lower for patients whose operations were delayed compared with those unresected.

Conclusions—Although EGC showed a relatively long natural history in general, it progressed to the advanced stage with time and led to death from gastric cancer for the most part if left untreated.

Keywords: early gastric cancer; natural history

Gastric cancer is still one of the major causes of cancer deaths, although mortality has been consistently decreasing. Early detection and early treatment are believed to be effective in reducing mortality from gastric cancer, especially in Japan, where the incidence of this disease is the highest in the world. In 1983, we presented data on the natural course of 43 early gastric cancer (EGC) cases and survival for 34 untreated EGC patients; we suggested that early diagnosis and early treatment may lead to a reduction in mortality from gastric cancer. The study comprised 56 cases who were diagnosed endoscopically as having EGC before 1976 but on whom surgical resection was not conducted or delayed for more than six months. These cases were followed up until November 1980. Recently, however, controversy has arisen on the natural history of EGC, implying that EGC is a pseudo-cancer which rarely progresses to an advanced stage. To examine the natural history of EGC more clearly, a non-concurrent, long term, follow up study was conducted in EGC patients on whom surgical resection was not conducted or delayed by more than six months after diagnosis. Special attention was paid to the study design so that sufficiently long follow up periods were studied.

Methods

STUDY SUBJECTS

Eligibility of study subjects was essentially the same as in the previous report in 1983: patients who were diagnosed endoscopically as having EGC, confirmed as cancer on biopsy, but in whom surgical or endoscopic resection was not conducted or delayed by more than six months (fig 1). To ensure long follow up periods of more than 10 years, the study was restricted to patients diagnosed before the end of October 1988 and followed up until the end of October 1998. Based on the hospital cancer registry of Osaka Medical Center for Cancer and Cardiovascular Disease (OMCC) and the screening detected EGC patients’ files kept at the Osaka Cancer Detection and Prevention Center (OCDPC), candidates for the study were systematically retrieved. These candidates were collated with the database of the Osaka cancer registry, a population based cancer registry covering all of Osaka prefecture since December 1962. A questionnaire was mailed to referred medical doctors or patients’ families, where possible, to confirm if they had undergone surgical resection or follow up examinations for gastric cancer. In addition to the 56 cases of the previous study in 1983, 15 patients were found to meet the above mentioned criteria. A total of 71 cases were eligible for this study. Vital status as of the end of October 1998 was assessed by referral to residential registrations of municipality offices. Causes of death were confirmed by death certificate.

Abbreviations used in this paper: EGC, early gastric cancer; OMCC, Osaka Medical Center for Cancer and Cardiovascular Disease; OCDPC, Osaka Cancer Detection and Prevention Center.
Eligibility of the study subjects:
Patients diagnosed endoscopically as having EGC and confirmed as cancer with biopsy, but on whom surgical or endoscopic resection was not conducted or delayed more than six months. Their diagnosis was done before October 1988.

Hospital cancer registry's file of OMCC
Screening detected EGC patients' file of OCDPC
Osaka cancer registry's file
Questionnaire to referred medical doctors
Questionnaire to patients or their family
Information on surgical resection or follow up examinations for gastric cancer
Information on vital status as of the end of October 1998

Study subjects and their outcome
• Natural courses of EGC were elucidated for 56 cases: 20 cases remained in the early stage
36 cases progressed to the advanced stage
• Survival analysis:
38 cases had never undergone surgical resection
35 died, 1 alive, 2 unknown for vital status
33 cases had undergone delayed surgical resection
26 died, 7 unknown for vital status

Results
For 56 of the total 71 study subjects, the natural course of EGC was elucidated through subsequent examinations with endoscopy and/or double contrast x ray, or pathological findings on postoperative material (fig 1). Over a period of 6–137 months (mean 39 months), 20 remained in the early stage while 36 progressed to the advanced stage. Figure 2 shows Kaplan-Meier estimates of the proportion remaining in the early stage. The proportion remaining in the early stage decreased consistently with time. Median duration of those who remained in the early stage was estimated as 44 months. Cumulative five year risk for progressing to the advanced stage was estimated as 63.0% (95% confidence interval (CI) 48.1–77.9%). Among the 56 cases, 27 were detected through screening programmes for gastric cancer while the remaining 29 were diagnosed at outpatient clinics by various symptoms. Age and sex adjusted hazard rate ratio for progressing to the advanced stage was 0.90 (95% CI 0.45–1.79; p=0.77) in the screening detected compared with the non-screening detected cases.

In 38 cases there was no evidence of surgical resection for gastric cancer, although in two of these cases vital status as of the end of October 1998 was unknown. During the follow up period of 13–207 months (mean 72 months), 35 cases had died while one patient was alive (fig 1). Twenty three died from gastric cancer while nine died from other causes. Cause of death was unknown for the remaining three cases. When these three cases were regarded as gastric cancer deaths, cumulative five year corrected survival of the 38 unresected cases was estimated as 62.8% (95% CI 46.6–79.0%). If these three were regarded as censored, the corrected survival rate was estimated at 67.8%. Among the 38 unresected cases, 18 were detected through screening programmes for gastric cancer while the remaining 20 were diagnosed at outpatient clinics by symptoms. When the three cases of unknown cause of death were regarded as gastric cancer deaths, the hazard rate ratio for gastric cancer mortality was 0.65 (95% CI 0.28–1.55; p=0.34) in the screening detected compared with the outpatient detected cases.

Concerning the 33 cases whose operations were delayed, 19 gastric cancer deaths and four deaths from other causes were observed, as well as three unknown causes of death, over a period of 10–213 months (mean 104 months). Vital status of the remaining seven cases was unknown as of the end of October 1998, although their living status had been confirmed 73–183 months (mean 122 months) after diagnosis of EGC (fig 1). The periods between diagnosis of EGC and surgical operation were 6–12 months in seven patients, 13–24 months in eight, 25–36 months in six, 37–48 months in two, 49–60 months in five, and more than 60 months in five. Postoperative findings of the lesions revealed advanced gastric cancer in 18 cases and early gastric cancer in 13. The remaining two were unknown. Their cumula-
endoscopy was reported to be 80% or more. However, diagnostic accuracy of EGC with stage from the start of the observation, therefore, might have been in the advanced having progressed to the advanced cancer, sis. Our study subjects who were diagnosed as mucosal or submucosal layers, pathological findings. As EGC is defined as adenocarcinoma where cancer invasion remains in the lamina propria. If it were applicable to the present study subjects, some borderline lesions of such adenomas and dyplasias, as might be observed only for 56 of the original 71 cases. Characteristics possibly relating to cancer progression were included. Subjects with well or moderately differentiated adenocarcinoma showed lower hazard rate ratios for progression to the advanced stage (hazard rate ratio for intestinal type EGC. The Japanese tended to diagnose gastric cancer even if there was no evidence of invasion into the lamina propria whereas Western pathologists never diagnosed cancer without invasion of the lamina propria. If it were applicable to the present study subjects, some borderline lesions of such adenomas and dyplasias, as might be termed by Western pathologists, have been included. Subjects with well or moderately differentiated adenocarcinoma showed lower hazard rate ratios for progression to the advanced stage (0.68 and 0.45, respectively) compared with those with undifferentiated or poorly differentiated adenocarcinoma but the differences were not significant. Furthermore, the study included a total of 36 cases that were detected through screening programmes for gastric cancer. Therefore, it is likely that the study subjects may have included rather slow growing cases in relation to length biased sampling or over diagnosis, as indicated in this study (hazard rate ratio for gastric cancer mortality was 0.65 in the screening detected cases). Despite these possibilities of misclassifications and biases, the results showed that EGC, if left untreated, would progress to the advanced stage and lead to death from gastric cancer. We consider that the effect on gastric cancer mortality in this study would have been underestimated. Thirdly, the results on the natural course of EGC may have been biased as they were observed only for 56 of the original 71 cases. Characteristics possibly relating to cancer progression were compared between the 56 cases and the remaining 16 cases. The proportion in the screening detected group was 48.2% among the former and 60.0% in the latter. The proportion of those with well or moderately differentiated adenocarcinoma was 59.6% and 63.6%, respectively. These findings suggest that the results obtained may have been biased towards rapid growing cases, but the magnitude of this bias does not appear to be important. Cause specific survival was further compared between the two groups using Cox regression analysis in which variables such as age, sex, history of gastrectomy, macroscopic type of EGC, and histology were included. The multivariate adjusted hazard rate ratio was 0.77 for the 56 cases, but not statistically different from 1.0.

It has recently been reported that diagnostic criteria for gastric cancer are different between Japanese and Western pathologists, in particular for intestinal type EGC. The Japanese tended to diagnose gastric cancer even if there was no evidence of invasion into the lamina propria whereas Western pathologists never diagnosed cancer without invasion of the lamina propria. If it were applicable to the present study subjects, some borderline lesions of such adenomas and dyplasias, as might be termed by Western pathologists, have been included. Subjects with well or moderately differentiated adenocarcinoma showed lower hazard rate ratios for progression to the advanced stage (0.68 and 0.45, respectively) compared with those with undifferentiated or poorly differentiated adenocarcinoma but the differences were not significant. Furthermore, the study included a total of 36 cases that were detected through screening programmes for gastric cancer. Therefore, it is likely that the study subjects may have included rather slow growing cases in relation to length biased sampling or over diagnosis, as indicated in this study (hazard rate ratio for gastric cancer mortality was 0.65 in the screening detected cases). Despite these possibilities of misclassifications and biases, the results showed that EGC, if left untreated, would progress to the advanced stage and lead to death from gastric cancer. Duration of EGC and survival of unresected EGC cases showed essentially the same results examinations had been in the advanced stage from the start of the study.
as our former study. In the present study, we attempted to examine the effect of delayed operation on mortality from gastric cancer because it was important to clarify if advocating surgical resection would still benefit the patient. The results suggested that EGC patients would still benefit even if surgery was delayed for more than six months after diagnosis. However, we would urge caution in this interpretation as those individuals who were in the delayed operation group had to survive long enough to have surgery. Thus this may have led to an overestimate of survival in the delayed surgery group. However, this is unlikely to have had a major effect on the results as few patients died quickly, and follow up was long compared with the time delay before surgery.

At present, there are several observational studies supporting the effectiveness of early detection and early treatment in reducing mortality from gastric cancer while others have argued against it. In their report, Everett and Axon claimed that EGC is a pseudo-disease, possibly based on the results of the study of von Holstein and colleagues. von Holstein and colleagues compared 354 postgastrectomy patients who accepted endoscopic screening with 484 who either declined or were not offered investigation. Over 17 years of follow up, 17 EGCs were detected in the screening group compared with two cases in the control group. The number of deaths from gastric cancer in the two groups was similar (12 v 14). The authors suggest that screening detected EGC is a pseudo-cancer. However, the study did not use random allocation, and thus it was possible that some bias affected the results. As the study subjects were all postgastrectomy patients, there is no guarantee that the study results are applicable to the general population. von Holstein et al commented only or were not significant of regular endoscopic screening for postgastrectomy patients.

Our long term follow up study, together with previously reported case control studies on the effectiveness of screening programmes, strongly suggest that early detection and early treatment are effective in reducing mortality from gastric cancer. To confirm this, however, it is necessary to conduct a randomised controlled trial of endoscopic screening of the general population. Endoscopic mucosal resection for gastric cancer has recently been developed. It is known to be safe and equivalent to surgical resection. In combining the present evidence, we conclude that resection, including endoscopic mucosal resection in cases of mucosal cancer, is the first choice for those patients who are diagnosed as having EGC through screening programmes.

We thank the Osaka cancer registry, the hospital cancer registry of OMCC, and the OCPDC for use of their databases, and Sachiko Endoh, Mayumi Miyamoto, and Yoko Kanoshita for obtaining information on study subjects and their prognosis. This study was supported in part by a grant for New 10-year Strategy for Cancer Control, Prevention of Cancer, from the Japanese Ministry of Health and Welfare.

Natural history of early gastric cancer: a non-concurrent, long term, follow up study
H Tsukuma, A Oshima, H Narahara, et al.

*Gut* 2000 47: 618-621
doi: 10.1136/gut.47.5.618

Updated information and services can be found at:
http://gut.bmj.com/content/47/5/618.full.html

These include:

**References**
This article cites 9 articles, 1 of which can be accessed free at:
http://gut.bmj.com/content/47/5/618.full.html#ref-list-1

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

Pancreatic cancer (588 articles)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/