

Research Article

Gastric adenoma: A high incidence rate of developing carcinoma and risk of metachronous gastric cancer according to long-term follow-up

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Running title: Long-term outcome of gastric adenoma

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Abstract

Introduction

Gastric adenomas are histologically defined as benign epithelial tumors. While some of them remain adenomas for a long time, others progress to carcinomas. However, long-term outcomes of such cases are not entirely clear. Here, we explored the risk factors and incidence of developing carcinoma from gastric adenoma as well as metachronous gastric cancer.

Methods

This study was conducted at a facility that adopted a follow-up strategy for gastric adenoma. Lesions histologically diagnosed as gastric intestinal-type adenomas between January 2004 and December 2016 were analyzed. Clinicopathological data were collected from patients' medical records, and histological changes from adenoma to carcinoma during endoscopic follow-up and risk factors of cancer development were evaluated.

Results

This study involved 409 lesions from 376 patients. The analysis of the development of gastric cancer from adenoma and metachronous gastric cancer was ultimately performed for 282 lesions from 258 patients and 269 lesions from 246 patients, respectively, due to different follow-up periods. The 5-year rate of carcinoma development was 34.0%. Risk factors for carcinoma development upon multivariate analysis were lesion size ≥ 15 mm and morphological depression. All cases with both factors developed gastric carcinoma, and 50.5% of those with either factor developed carcinoma within 5 years. Gastric adenoma was accompanied by metachronous gastric cancer in 1.5% of the patients annually. The only risk factor for metachronous gastric carcinoma was primary adenoma progressing to carcinoma during the follow-up period.

Discussion/Conclusion

Given the high rate of carcinoma development in patients with risk factors, resection of gastric adenoma should be considered during the initial examination. Careful observation and follow-up should also be conducted to detect not only changes in the primary adenoma but also the occurrence of metachronous carcinoma, especially in cases of adenoma progressing to carcinoma.

Introduction

The World Health Organization (WHO) has defined gastric adenomas as circumscribed benign neoplasms composed of tubular and/or villous structures lined by dysplastic epithelium [1]. The two categories of gastric dysplasia (adenoma) are intestinal and gastric types, according to the 2019 WHO classification [2]. Intestinal-type adenomas arise in the mucosa that is severely inflamed due to *Helicobacter pylori* (*H. pylori*) infection, as well as due to intestinal gastric cancer [3]. Typical morphological characteristics of intestinal-type adenomas are flat, elevated whitish tumors located on the mucosa with atrophic gastritis or intestinal metaplasia. In contrast, gastric-type adenomas are likely to develop on the upper and middle body of the stomach with or without atrophic gastritis, and many are villous, elevated lesions, or elevated lesions with a smooth surface and constriction [4]. These two types of adenomas are thus quite different. As gastric-type adenomas are rare, adenomas in the stomach that are usually detected by esophagogastroduodenoscopy (EGD) screening in Japan have mainly been the intestinal type.

Adenomas in the colon are recognized as precancerous lesions in the oncogenic pathway of the adenoma-carcinoma sequence [5], and their endoscopic resection (ER) is generally performed worldwide to prevent colon cancer. In contrast, gastric intestinal-type adenomas are considered benign epithelial tumors, and while some may progress to cancer during the follow-up period, others remain adenomas for a long time [6,7]. Several reports have described the malignant development of gastric adenoma, with incidence rates ranging from extremely rare to approximately 20% [7,8,9]. The rate of malignant development of high-grade adenoma has been reported to be 60%-85% [10,11]. However, only a few studies have been conducted regarding long-term follow-up of gastric adenomas to assess their outcomes. The need for resection is controversial at present, and clinical treatment depends on the facility to which a patient is admitted. Furthermore, the incidence of metachronous gastric cancer after ER for gastric adenomas has been reported [12], but few reports have described the detailed occurrence of metachronous cancer in cases of gastric adenoma.

Since all cases of gastric intestinal-type adenoma are followed by annual EGD in our facility, except for cases in which carcinoma is highly suspected based on the clinical or histological findings, the long-term follow-up data were available for investigation. Therefore, in the present study, we explored the risk factors and incidence rate of developing carcinoma from intestinal-type gastric adenoma by investigating the long-term follow-up data.

Materials and Methods

Patients and lesions

Patients with gastric adenoma that was histologically diagnosed by an endoscopic forceps biopsy based on the Japanese diagnostic framework for a forceps biopsy [13] from January 2004 to December 2016 at the Okayama University Hospital were enrolled. We excluded patients with remnant stomach, gastric tube reconstruction, familial adenomatous polyposis, and gastric-type adenoma.

Clinical treatment strategy for gastric intestinal-type adenoma

The treatment strategy for gastric intestinal-type adenomas consists of annual follow-ups with EGD in our facility. When a lesion was diagnosed histologically as Grade 4 or 5 based on the Japanese diagnostic framework for a forceps biopsy during follow-up, ER was performed on the lesion at that time. The lesions recommended to receive ER by a conference of certified endoscopists also received ER, even when histologically diagnosed as Grade 3.

Data collection

The following clinicopathological data were collected from patients' medical records: age, sex, number of lesions, tumor size, macroscopic type, histological findings, status of *H. pylori* infection, atrophic gastritis, and comorbidity of gastric cancer.

H. pylori infection was diagnosed on the basis of positive results for at least one of the following tests: serum *H. pylori* IgG antibody test, stool antigen test, culture test, histological examination, urea breath test, or rapid urease test. The patients were classified into four groups based on the *H. pylori* infection status at the time of the diagnosis of gastric adenoma. Patients with positive results for any of the tests were classified as having a "current" infection, those with negative results for all but endoscopically diagnosed with atrophic gastritis were classified as having a "past" infection, those with negative results for all and no atrophic gastritis were classified as "uninfected," and those who were not tested for *H. pylori* infection were classified as "unknown".

The extent of atrophic gastritis was diagnosed by endoscopic findings and classified into four categories based on the Kimura-Takemoto classification [14]. Patients with no atrophic gastritis were classified as "none," those with C1-2 atrophic gastritis were classified as "mild," those with C3-O1 atrophic gastritis were classified as "moderate," and those with O2-3 atrophic gastritis were classified as "severe".

The comorbidity of gastric cancer was classified into three groups. Patients with gastric cancer diagnosed prior to the diagnosis of gastric adenoma were classified as having a "past" diagnosis, those diagnosed within one year after the diagnosis of gastric adenoma were classified as

having a “concurrent” diagnosis, and those diagnosed more than one year after the diagnosis of gastric adenoma were classified as being diagnosed “during follow up.”

Histological evaluation

Biopsy tissues and endoscopically resected specimens were routinely fixed with formalin and completely embedded in paraffin. Tissue blocks were sectioned to thin specimens, routinely processed, and stained with hematoxylin-eosin (HE). The prepared specimens made from biopsy tissues that were sliced into one or more pieces and those made from ER sliced every 2 mm based on the Japanese Classification of Gastric Carcinoma [13] were evaluated. All tissues were evaluated by two or more certified pathologists by HE staining based on the Japanese diagnostic framework for a forceps biopsy.

Evaluation of endoscopic images

The following endoscopic findings were reviewed by five expert endoscopists who had no information about which cases developed carcinoma: tumor size, morphological type, redness, and the change in these factors between the initial and latest endoscopy. If the evaluations differed among the experts, the final decision was made by the majority voting.

Morphological types were classified into protruded (0-I), superficial elevated (0-IIa), and flat (0-IIb) based on the Paris endoscopic classification. Lesions with any depressed areas were classified as depressed (0-I+IIc, 0-IIa+IIc, and 0-IIc). Lesions with a ≥ 5 mm increase in diameter during follow-up were defined as increased, and those with the appearance of depression or a reddish color were defined as morphologically changed.

Outcomes

- The analysis of the development of gastric carcinoma from adenoma

To analyze the development of gastric carcinoma from adenoma, we excluded cases with less than one year of endoscopic follow-up, except for cases of patients who underwent ER within one year following the initial diagnosis. Lesions for which the diagnosis was histologically changed to gastric carcinoma based on a biopsy or the examination of resected specimens were defined as cases of cancer development. The risk factors for the development of carcinoma were analyzed using the age, sex, location, diameter, macroscopic type, reddish color, enlargement during follow-up, emergence of depression, and appearance of redness of lesions. The Kaplan-Meier method was also used to analyze the occurrence rate of the development of gastric cancer from adenoma over time.

- The analysis for metachronous gastric carcinoma

To analyze metachronous gastric cancer, we excluded cases with less than one year of endoscopic follow-up. Newly occurring cases of gastric cancer showing coexistence with primary gastric adenoma were defined as metachronous gastric carcinoma. A risk factor analysis for metachronous gastric cancer and the Kaplan-Meier method were also used to analyze the occurrence rate of metachronous gastric cancer over time.

Statistical analyses

Data analyses were performed using the JMP Pro version 12 (SAS Institute Inc., Cary, NC, USA) software program, and continuous variables were represented as the median and range. Fisher's exact test was used for categorical variables, and logistic regression was used for continuous variables. The cut-off points of the lesion size at the initial diagnosis were determined through a receiver operating characteristics analysis. The Kaplan-Meier method was used to analyze the malignant transformation rate of adenoma during the study period. Statistical significance was defined as $P < 0.05$.

Results

Patient and lesion characteristics

This retrospective study included a total of 409 lesions in 376 patients. Table 1 shows the characteristics of all patients and lesions. The median age was 73 years, with mostly men enrolled (272/376, 72%). With regard to *H. pylori* infection, the majority of cases had been infected previously, and most had moderate or severe atrophic gastritis (363/376, 97%). A total of 129 patients (34%) were found to have developed cancer at other sites at any period. Lesion sites were classified as U (upper third), M (middle third), and L (lower third) in 6%, 61%, and 33%, respectively. The median diameter of lesions was 10 mm, and the typical morphological type was superficial and elevated, accounting for 87.8% of cases.

Patient flow in the long-term follow-up analysis

Of the 409 lesions in 376 patients, 127 lesions in 118 patients were followed for less than 1 year (excluding cases that underwent ER within 1 year); therefore, these cases were excluded from the analysis of cancerization of gastric adenoma. In addition, 140 lesions in 130 patients had been followed for less than 1 year, so these cases were excluded from the analysis of metachronous cancerous lesions (shown in Fig. 1).

Development of gastric carcinoma from adenoma

The development of gastric cancer from adenoma was ultimately analyzed for 282 lesions in 258 patients. Of these, 37 lesions were resected within 1 year because the lesions had been diagnosed with cancer or suspected cancer (Group 5, Group 4, or recommended resection by pathologist) at the biopsy on follow-up endoscopy in 33 cases. The lesions were located close to other gastric cancers and were resected at the same time in two cases, and the lesions were strongly suspected of being cancerous based on endoscopic findings, and the patients was recommended to undergo resection by an endoscopist conference in two cases. During the median observation period of 3.8 years (0.2-14.6), there were 80 lesions (28.4%) with cancer development, and 34.0% showed cancer development after 5 years according to the Kaplan-Meier analysis. Although the rate of carcinoma development in the first year was extremely high, the annual incidence of gastric adenoma was approximately 6.8% (shown in Fig. 2. a).

Endoscopic submucosal dissection (ESD) was performed in 75 of 80 lesions diagnosed as cancerous. Regarding the depth of the resected lesions, 74 lesions (99%) were intramucosal cancer, and curative resection was performed, while one lesion was submucosal invasive cancer, and non-curative resection was performed (shown in Fig. 3).

Results of the risk factor analysis

Univariate and multivariate analyses were performed to determine which factors were associated with the development of gastric carcinoma from adenoma (Table 2). Univariate analyses revealed that a lesion size ≥ 15 mm, macroscopic depression, reddish color, emergence of depression, and appearance of redness were associated with the development of carcinoma. Multivariate analyses revealed that a lesion size ≥ 15 mm and macroscopic depression were factors that were significantly associated with the development of gastric carcinoma from gastric adenoma.

All cases with both of these factors developed gastric carcinoma. The Kaplan-Meier analysis for the groups with and without either of the risk factors (size ≥ 15 mm or depression) showed that the rate of carcinoma development was significantly higher in the group with at least one risk factor (50.5% within 5 years, as shown in Fig. 2. b).

Metachronous gastric carcinoma during follow-up

The occurrence of metachronous cancerous lesions was ultimately analyzed for 269 lesions in 246 patients. A total of 23 carcinoma lesions in 17 patients were found at other sites during the follow-up period. As the number of events was small, only a univariate analysis was performed. Only the development of gastric cancer from adenoma was found to be significantly related to metachronous gastric cancers (Table 3).

Regarding the treatment, endoscopic mucosal resection was performed for one lesion, ESD for 21 lesions, and surgery for one lesion, with curative resection obtained in 22 lesions. The occurrence of cancer at other sites was observed in 6.9% of patients with a median observation period of 3.8 years and was recognized in 7.0% at 5 years using the Kaplan-Meier method (shown in Fig. 4). The annual incidence of metachronous gastric cancer was approximately 1.5% in this study.

Discussion/Conclusion

In our study, the 5-year rate of developing carcinoma from gastric intestinal adenoma was 34.0%. The risk factors were a lesion size ≥ 15 mm and morphological depression. All cases with both factors developed gastric carcinoma, and 50.5% of those with either factor had developed carcinoma at 5 years. Therefore, it should be recognized that gastric adenoma carries a high risk of progressing to carcinoma and an accurate treatment strategy needs to be considered on the basis of the presence of these risk factors. In addition, 1.5% of patients with gastric adenoma developed metachronous gastric cancer each year.

In a previous report, the characteristics that were related to the development of gastric carcinoma from adenoma were large lesion size, depression, and redness [15–17]. In addition, enlargement and morphological changes during follow-up are often recognized in cancerous gastric adenoma lesions [18]. In the present study, however, the only factors that were related to the development of carcinoma from gastric adenoma were a lesion size ≥ 15 mm and a depressed morphological type. As the endoscopic findings of these factors were reviewed by five expert endoscopists, we believe that our results might better represent the actual situation, despite the retrospective nature of our study. Although these risk factors were identified in this study, pathological factors, such as severe atypia, are also known as risk factors [19]. However, in our study, the diagnosis was based on the use of a group classification, and, as a result, we cannot mention the risk factors for severe atypia.

Furthermore, 50.5% of lesions with either factor had developed carcinoma at 5 years according to the Kaplan-Meier method. These lesions had a higher risk of developing cancer than those with no risk factors. Since both of these risk factors can be detected at the initial examination, cases with both factors should be treated carefully while considering the possibility of cancerous lesions and the need for ER. Many of these lesions progressed into cancer within one year, but these lesions were not diagnosed as gastric cancer at the time of initial diagnosis. This phenomenon may be due to the pathological difficulty of distinguishing between adenoma and carcinoma based on the evaluation of only small biopsy specimens. However, the pathological diagnosis of whether a lesion is adenoma or cancer is important for clinicians because the treatment strategy of the lesion changes significantly depending on the diagnosis. From our data, we conclude that a close follow-up for one year after the initial diagnosis is necessary, especially in patients with various risk factors, because the diagnosis may change to cancer on follow-up examinations.

During the follow-up, most lesions that progressed to carcinoma could be cured by ESD. However, one lesion had invaded the deep submucosal layer (SM2), leading to non-curative resection. This lesion was over 15 mm in size. According to the results of our risk factor analysis, this lesion should have been resected at the initial diagnosis. When considering the treatment strategy for cases

of low-risk cancerization, we should weigh the patient's condition and cancerization risk. However, based on our present findings, we should consider the possibility of not achieving a cure by ER during follow-up. We recommend resection for lesions with either of the risk factors.

The incidence rate of metachronous gastric cancer of gastric adenoma was reported to be 1.5% per person-year [20]. In our study, the incidence rate of metachronous gastric cancers was 1.5% per person-year during the follow-up period. Severe atrophic gastritis has been reported to be a risk factor for the development of metachronous gastric cancer [21,22]. However, no significant relationship was noted between atrophic gastritis and metachronous gastric cancer in the present study. The only risk factor for metachronous gastric cancer was the development of carcinoma from gastric adenoma. Metachronous gastric cancer after ER of gastric carcinoma was reported to occur at a rate of 0.9-4.8% per person-year [23–26]; hence, patients with a history of ER of gastric carcinoma were regarded as a high-risk cohort for metachronous gastric cancer. Therefore, our finding that metachronous gastric cancer was more likely to occur in patients with gastric adenoma that changed to gastric cancer than in others is easily justified. However, even in cases with gastric adenoma that did not change to carcinoma, the incidence rate of metachronous gastric cancer was relatively high. Consequently, patients with gastric adenoma should be recognized as having a high risk of cancerization at other sites.

Several limitations associated with the present study need to be mentioned. First, lesions with risk factors tended to be treated early, as endoscopists tend to re-examine such lesions within one year. Increasing the number of biopsies increases the chances of being diagnosed with cancer and may therefore lead to selection bias. Second, the histological diagnosis depended on the pathologist; however, this bias is thought to be minimized since all diagnoses were confirmed by two or more pathologists from our facility. Third, this study was retrospective and conducted at a single facility, so further prospective studies at multiple facilities are necessary.

In conclusion, the risk factors for the progression of gastric adenoma to carcinoma were a lesion size ≥ 15 mm and macroscopic depression. Given the high rate of carcinoma development in patients with these risk factors, resection of gastric adenoma should always be considered. In addition, careful observation and follow-up should also be conducted to detect not only changes in the primary adenoma but also the occurrence of metachronous carcinoma, especially in cases of adenoma progressing to carcinoma.

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Statement of Ethics

Informed consent was obtained from the patients for the use of their clinical data using an opt-out method. The study protocol has been approved by the ethics committees of Okayama University Hospital (REFERENCE number : 1808-010), and this study was conducted according to the Declaration of Helsinki.

Conflict of Interest

The authors declare no conflicts of interest in association with the present study.

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Author Contribution

Y.O. and H.K.: designed the study. Y.O., H.K., H.S, M.A., and M.I.: acquired data. T.T., S.K., Y.K., and H.O.: advised for this study. Y.O. and H.K.: analyzed the data. Y.O and H.K.: wrote the paper; all authors read and gave approval of the final version of the article to be published.

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Figure Legends

Fig. 1. Patient flow.

Fig. 2. a Kaplan-Meier analysis for the development of gastric carcinoma from adenoma.

Fig. 2. b Kaplan-Meier analysis for the development of gastric carcinoma from adenoma with or without risk factors.

Fig. 3. Lesions of SM developing cancer.

Fig. 3. a A 30-mm protruding lesion was detected on the gastric anterior wall of the middle area at the initial examination. The lesion was histologically diagnosed as adenoma by a forceps biopsy.

Fig. 3. b One year later, the lesion had widely spread, and the histological diagnosis was changed to suspected cancer (Group 4) by an endoscopic biopsy.

Fig. 3. c The lesion underwent ESD, and complete resection was achieved (yellow line in Fig. 3. d)

Fig. 3. d The lesion was diagnosed as carcinoma with deep submucosal invasion, resulting in non-curable resection.

Fig. 4. Kaplan-Meier analysis of metachronous gastric cancer.