Four Endoscopic Predictors of Carcinoma as a Final Diagnosis after Endoscopic Resection of Forceps Biopsy-proven Gastric Adenomas

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Background/Aims: Previous studies have reported that the frequency of re-diagnosing as carcinoma after endoscopic resection of gastric adenoma ranges between 6% and 47%. Therefore, specific endoscopic findings have been used to predict re-diagnosing as carcinoma after endoscopic resection of gastric adenoma at our center. We evaluated whether there is a use for these indicators for predicting carcinoma as a final diagnosis in forceps biopsy-proven adenomas.

Materials and Methods: We investigated 378 tissue samples from 308 patients. Classification of specimens as adenoma and carcinoma was based on postresection specimen. Endoscopic findings were reviewed for tumor location, size, gross appearance, surface nodularity, central concavity, surface color, and presence of ulcers. These variables were analyzed and compared between the adenoma group (275 cases) and the carcinoma group (103 cases), assigned based on post-resection diagnosis.

Results: The mean patient age was 61, and 227 of the patients were male. The mean lesion diameter was 14.9±8.1 mm in the adenoma group and 17.9±9.3 mm in the carcinoma group. A lesion size of 15 mm or greater, depressed appearance, surface nodularity, central concavity, and presence of high-grade dysplasia were all independently associated with re-diagnosing as carcinoma after endoscopic resection.

Conclusions: Lesion size of 15 mm or greater, depressed-type appearance, central concavity, and nodular surface are feasible predictors of carcinoma as a final diagnosis in forceps biopsy-proven adenomas. Physicians need to recommend immediate endoscopic resection for forceps biopsy-proven adenomas with these four independent features so as not to miss the optimal window for treatment. (Korean J Helicobacter Up Gastrointest Res 2013;13:36-43)

Key Words: Stomach; Adenoma; Carcinoma; Endoscopic; Treatment

INTRODUCTION

Although technological advances have made endoscopic resection for the treatment of gastric adenoma more common, many patients and caregivers, particularly those in rural areas, still hesitate to pursue this option, reasoning that the adenoma does not pose any current risks to their life. Physician decisions are informed by pathologic report results from forceps-biopsied specimens. Therefore, reliable histological results from forceps biopsies are essential in planning appropriate treatment strategies.

Previous studies have reported rates of re-diagnosing as carcinoma following resection ranging from 6% to 47%.1-3 Accurate diagnosis and classification of epithelial neoplasms requires whole specimens; this discrepancy is therefore inevitable, as forceps biopsies obtain only small parts of the entire lesion.4-6 Recent research has shown that advanced endoscopic imaging technology may be useful in diagnosing gastric epithelial neoplasm more precisely before dissection.7-9 However, these technologies are limited by their availability at only few institutions, their need for special training for operation, and their novelty which warrants more investigation into their utility.

Therefore, predictors of re-diagnosing as carcinoma based on white light endoscopic images may be more valuable and practical for the majority of endoscopists. No previous studies have found specific endoscopic findings independently predicted re-diagnosing as carcinoma after resection, with the exception of one that identified depressed-type appearance as a predictor.10-13 Based on our experience, we hypothesize that carcinoma as a final diagnosis may be predicted in forceps biopsy-
proven (FBP) adenomas based on endoscopic features such as gross appearance, color, presence of ulcerative lesions, and surface pattern (i.e., nodularity or concavity), even though inconsistent data have appeared in the literature as predictive factors of re-diagnosing as carcinoma.10-12 Herein, we investigate whether these specific endoscopic findings are statistically valuable for predicting carcinoma as a final diagnosis in FBP adenomas.

**MATERIALS AND METHODS**

1. Patients and specimens

All patients who underwent endoscopic resection for FBP adenoma of the stomach between January 2004 and May 2012 at Gospel Hospital, Kosin University College of Medicine were retrospectively reviewed consecutively. The study protocol was approved by our institutional review board (KUGH IRB 12-059). Gastric adenomas with different grades of dysplasia (low or high) were diagnosed in all cases and confirmed as either gastric adenoma or gastric carcinoma after endoscopic resection. The cases were divided into an adenoma group and a carcinoma group according to final diagnosis based on the histology of the post-resection specimen.

2. Endoscopic resection and histologic evaluation

After visualization of the gastric adenoma, marks were made 5 mm outside the tumor edge with an argon plasma coagulator (PSD-60, Olympus, Tokyo, Japan). Hypertonic saline mixed with epinephrine (1:100,000 solution) was injected into the submucosal layer to produce a submucosal cushion. The lesion was incised along the outer border of the marked lesion using a flex knife (KD-610L, Olympus). The lesion then was resected with a snare (endoscopic mucosal resection) or dissected (endoscopic submucosal dissection) with an insulation tipped diathermic knife (KD-610L). Resected specimens were washed in normal saline, oriented with small pins, fixed in 8% formaldehyde solution, and embedded in paraffin. The tissues were sliced into 2 mm sections and submitted for histologic diagnosis. One pathologist reviewed the specimens obtained by forceps biopsy and endoscopic resection. The diagnosis was...
determined on the basis of recent criteria for gastric dysplasia and carcinoma. Combined findings of adenoma and carcinoma were classified as a carcinoma.

3. Evaluation of endoscopic features

Endoscopic films and reports were reviewed for tumor location, size, gross appearance (elevated, flat, depressed), central concavity, surface nodularity, surface color, and the presence of ulcerative lesions (Fig. 1). The longitudinal locations of the tumors were defined as appearing in the upper, middle, or lower third of the stomach. The circumferential locations of the tumors were described as anterior wall, posterior wall, lesser curvature, or greater curvature. Gastric neoplasms were classified macroscopically according to the Japanese classification system. Type 0-I (protruded) and type 0-IIa (superficially elevated) were grouped together in our study as “elevated”. Type 0-IIb was grouped as “flat”. Type 0-IIc (superficially depressed), and type 0-IIa+IIc (elevated with central depression) were grouped together as “depressed.” These parameters were compared between the adenoma group and the carcinoma group.

4. Statistical analysis

Univariate analyses were performed using independent t-tests to compare the age of the patients and the size of the adenomas. Other categorical data were analyzed using the chi-square test (SPSS ver. 16.0, SPSS Inc., Chicago, IL, USA). Statistical significance was set at \( P < 0.05 \), and if univariate analysis revealed more than one predictor with statistical significance, multivariate analysis using a logistic regression model was performed. We also analyzed Wald value, Exp (B), sensitivity, specificity, positive predictive value, negative predictive value for all independent predictive factors.

RESULTS

1. General characteristics

We reviewed the data of 308 patients (227 men and 81 women) with 378 FBP adenomas from January 2004 to May 2012. The mean (±SD) age of the patients was 61.1±9.2 years (range, 31~71). The mean interval (±SD) from forceps biopsy to endoscopic resection was 27.9±26.4 days (range, 8~196). Endoscopic resection was performed within 90 days of forceps biopsy in 96% of the FBP adenomas.

2. Endoscopic and histologic characteristics of FBP adenomas (Table 1)

The mean (±SD) size of FBP adenomas was 15.8±8.5 mm (range, 5~50), and 50.8% of the 378 FBP adenoma lesions were larger than 15 mm in diameter. The most common longitudinal location of FBP adenomas was in the lower third of the stomach (226 cases, 59.8%), and the posterior wall was the most common circumferential location.

| Variable                     | Tissue sample (n=378) |
|------------------------------|-----------------------|
| Size                         | 15.8±8.5              |
| Size≥15 mm                   | 192 (50.8)            |
| Gross appearance             |                       |
| Elevated                     | 309 (81.7)            |
| Flat                         | 7 (1.9)               |
| Depressed                    | 62 (16.4)             |
| Ulcerative lesion            | 17 (4.5)              |
| Central concavity            | 97 (25.7)             |
| Reddish color                | 156 (41.3)            |
| Nodular surface              | 104 (27.5)            |
| Location                     |                       |
| Longitudinal                 |                       |
| Upper third                  | 28 (7.4)              |
| Middle third                 | 124 (32.8)            |
| Lower third                  | 226 (59.8)            |
| Circumferential              |                       |
| Anterior wall                | 84 (22.2)             |
| Posterior wall               | 113 (29.9)            |
| Lesser curvature             | 104 (27.5)            |
| Greater curvature            | 77 (20.4)             |
| Clinical impression by endoscopic findings |   |
| Adenoma                      | 243 (64.3)            |
| Carcinoma                    | 84 (22.2)             |
| Othersa                       | 51 (13.5)             |
| Grade of dysplasia in forceps-biopsy specimens |   |
| High-grade dysplasia         | 72 (19.0)             |
| Low-grade dysplasia          | 306 (81.0)            |
| Kinds of endoscopic resection|                       |
| Endoscopic mucosal resection | 258 (68.3)            |
| Endoscopic submucosal dissection | 120 (31.7)         |

Values are presented as n (%) or mean±SD.

aOthers includes 34 raised erosions, 7 hyperplastic polyps, 5 benign gastric ulcers, and 5 intestinal metaplasias.
location (113 cases, 29.9%). Forceps biopsy specimens suggested that 19% of the lesions were high-grade dysplasia and 81% were low-grade dysplasia. Regarding treatment, 258 (68.3%) FBP adenomas were removed by endoscopic mucosal resection and 120 (31.7%) lesions were treated by endoscopic submucosal dissection.

3. Discrepancy in histologic diagnoses between forceps biopsy specimens and post-resection specimens (Table 2)

After resection, examination of a 2-mm section of the whole specimen revealed that the concordance rate between the forceps biopsy samples and the post-resection specimens was 62.2% (235 of 378 cases). The rate of complete agreement according to the grade of dysplasia in FBP adenomas was 13.9% for high-grade dysplasia (10/72) and 73.5% for low-grade dysplasia (225/306). Although the initial histologic diagnosis of some forceps biopsy specimens was low-grade dysplasia, some were found to be high-grade dysplasia (5.9%) or carcinoma (20.6%) in post-resection diagnosis (Fig. 2). Conversely, initial diagnosis of high-grade dysplasia was later con-

Table 2. Comparison of Histologic Diagnosis between Forceps Biopsy Specimen and Postresection Specimen

| Tissue sample (n=378) | Adenoma (n=275) | Carcinoma (n=103) | Postresection diagnosis |
|-----------------------|----------------|-------------------|------------------------|
|                       | High grade dysplasia | Low grade dysplasia | Poor | Mod | Well | Total |
| FBP adenomas          |                 |                   |       |     |      |      |
| High-grade dysplasia  | 10 (2.7)        | 22 (5.8)          | 1 (0.3) | 6 (1.6) | 33 (8.7) | 72 (19.0) |
| Low-grade dysplasia   | 18 (4.8)        | 225 (59.5)        | 0 (0.0) | 15 (4.0) | 48 (12.7) | 306 (81.0) |
| Total                 | 28 (7.4)        | 247 (65.3)        | 1 (0.3) | 21 (5.6) | 81 (21.4) |      |

Values are presented as n (%).

Poor, poorly differentiated; Mod, moderately differentiated; Well, well differentiated; FBP adenoma, forceps biopsy-proven adenoma.

Fig. 2. Carcinomatous transformation from a forceps biopsy-proven adenoma after endoscopic resection. (A) An about 1.5 cm sized, slightly elevated lesion (arrowheads) with central depression (arrows) was observed at the greater curvature of the proximal antrum. (B) Forceps biopsy showed adenoma with low-grade dysplasia (H&E, ×400). (C) Postresection histologic evaluation revealed carcinoma component (red line) and adenoma component with low-grade and high-grade dysplasia (blue line) (H&E, ×100).
firmed as low-grade dysplasia (30.6%) or early gastric cancer (55.6%) in the final pathologic diagnosis after resection. Regarding re-diagnosing carcinoma at post-resection diagnosis, the diagnosis of FBP adenomas was changed to carcinoma in nearly one third of the cases (103 cases, 27.2%). Of these, one case was poorly differentiated, 21 cases were moderately differentiated, and 81 cases were well-differentiated.

4. Endoscopic and pathologic features between the adenoma and carcinoma groups at post-resection diagnosis (Table 3)

There were no differences between the adenoma and carcinoma groups in age, sex, or interval from forceps biopsy to endoscopic resection. The size of the lesion in the carcinoma group was significantly larger than that in the adenoma group (18.4±8.0 mm vs. 14.8±8.0 mm, P<0.001), and lesions 15 mm or greater were more frequently observed in the carcinoma group (72/103 cases, 69.9% vs. 120/275 cases, 43.6%; P<0.001). Depressed lesions were more common in the carcinoma group (25/103 cases, 24.3% vs. 37/275 cases, 13.5%; P=0.014). Central concavity, ulcerative lesion, reddish color, and nodular surface each showed tight correlation with carcinoma at post-resection diagnosis (P=0.008, P<0.001, P<0.001, and P=0.006 respectively). Regarding location, no specific site was associated with re-diagnosing carcinoma at post-resection diagnosis. The presence of high-grade dysplasia in FBP adenomas was a risk factor for re-diagnosing carcinoma at post-resection diagnosis (P<0.001). Overall endoscopic impression, before reported forceps-biopsy results, was significant factors for understanding final diagnosis after resection (P<0.001).

5. Multivariate analysis of endoscopic and histologic features associated with potential malignancy after resection (Table 4)

Multivariate analysis including the variables of size, gross appearance, central concavity, ulcerative lesion, mucosal color, nodularity, and high-grade dysplasia in forceps biopsy specimens was performed. Overall endoscopic impression was not included in multivariate analysis because these impressions were decided by analyzing each factor but by each endoscopist’s preference. Analysis revealed that size 15 mm or greater, depressed appearance, central concavity, nodular surface, and high-grade dysplasia in forceps biopsy specimens were independent variables predicting carcinoma as a final diagnosis. Among all four endoscopic risk factors, size ≥15 mm was the most influential [Wald=13.008, P<0.001, Exp (B)=2.747, 95% CI=1.586~4.756] and had the greatest sensitivity (0.69) and negative predictive value (0.83). Depressed appearance had the highest specificity (0.86).

Table 3. Comparison of Endoscopic and Histologic Features between Adenoma and Carcinoma Groups at Postresection Diagnosis in Forceps Biopsy-Proven Adenomas

| Tissue sample (n=378) | Adenoma (n=275) | Carcinoma (n=103) | P value |
|-----------------------|----------------|------------------|---------|
| Age (yr)              | 60.3±8.9       | 62.2±14.4        | 0.122   |
| Male                  | 194 (70.5)     | 80 (77.7)        | 0.127   |
| Interval from forcep-biopsy to endoscopic resection (day) | 28.3±27.7 | 26.8±22.7 | 0.691 |
| Size (mm)             | 14.8±8.0       | 18.4±9.3         | <0.001  |
| Size ≥15 mm           | 120 (43.6)     | 72 (69.9)        | <0.001  |
| Gross appearance      |                |                  |         |
| Elevated              | 231 (84.0)     | 78 (75.7)        | 0.014   |
| Flat                  | 5 (1.8)        | 2 (1.9)          |         |
| Depressed             | 37 (13.5)      | 25 (24.3)        |         |
| Ulcerative lesion     | 11 (4.0)       | 16 (15.5)        | <0.001  |
| Central concavity     | 60 (21.8)      | 37 (35.9)        | 0.008   |
| Reddish color         | 103 (37.5)     | 53 (51.5)        | 0.014   |
| Nodular surface       | 65 (23.6)      | 39 (37.9)        | 0.006   |
| Location              |                |                  |         |
| Longitudinal          |                |                  |         |
| Upper third           | 19 (6.9)       | 9 (8.7)          | 0.115   |
| Middle third          | 98 (35.6)      | 26 (25.2)        |         |
| Lower third           | 158 (57.5)     | 68 (66.0)        |         |
| Circumferential       |                |                  |         |
| Anterior wall         | 59 (21.5)      | 25 (24.3)        | 0.433   |
| Posterior wall        | 79 (28.7)      | 34 (33.0)        |         |
| Lesser curvature      | 82 (29.8)      | 22 (21.4)        |         |
| Greater curvature     | 55 (20.0)      | 22 (21.4)        |         |
| Forceps biopsy number | 3.6±1.2        | 4.1±2.0          | 0.058   |
| Histologic grade      |                |                  |         |
| High-grade dysplasia  | 32 (11.6)      | 40 (38.8)        | <0.001  |
| Low-grade dysplasia   | 243 (88.4)     | 65 (61.2)        |         |
| Kinds of endoscopic resection |        |                  |         |
| Endoscopic mucosal resection | 184 (66.9) | 74 (71.8) | 0.387 |
| Endoscopic submucosal dissection | 91 (33.1) | 29 (28.2) |         |
| Endoscopic impression |                |                  |         |
| Adenoma               | 203 (73.8)     | 40 (38.3)        | <0.001  |
| Carcinoma             | 37 (13.5)      | 47 (45.6)        |         |

Values are presented as n (%) or mean±SD.
Table 4. Multivariate Analysis of the Endoscopic Features and Histologic Result of Potential Malignancy after Resection

| Risk factor           | Wald  | P value | Exp (B) (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | Positive predictive value (95% CI) | Negative predictive value (95% CI) |
|-----------------------|-------|---------|------------------|----------------------|----------------------|-----------------------------------|-----------------------------------|
| Size ≥ 15 mm          | 13.008| <0.001* | 2.747 (1.586~4.756) | 0.69 (0.59~0.78)     | 0.56 (0.50~0.62)     | 0.38 (0.31~0.45)                  | 0.83 (0.77~0.88)                   |
| Depressed type        | 9.055 | 0.001*  | 2.494 (1.375~4.522) | 0.24 (0.17~0.34)     | 0.86 (0.82~0.90)     | 0.40 (0.28~0.34)                  | 0.76 (0.70~0.79)                   |
| Ulcerative lesion     | 0.799 | 0.055   | 1.124 (0.950~3.343) | 0.69 (0.59~0.78)     | 0.69 (0.59~0.78)     | 0.56 (0.50~0.62)                  | 0.83 (0.77~0.88)                   |
| Central concavity     | 9.055 | 0.003*  | 2.654 (1.472~4.785) | 0.56 (0.27~0.46)     | 0.78 (0.73~0.83)     | 0.38 (0.29~0.49)                  | 0.77 (0.71~0.81)                   |
| Reddish color         | 0.388 | 0.533   | 1.188 (0.690~2.046) | 0.56 (0.28~0.48)     | 0.56 (0.50~0.62)     | 0.38 (0.29~0.48)                  | 0.77 (0.71~0.81)                   |
| Nodular surface       | 8.034 | 0.005*  | 2.307 (1.294~4.112) | 0.38 (0.28~0.48)     | 0.76 (0.71~0.81)     | 0.38 (0.28~0.48)                  | 0.77 (0.71~0.81)                   |
| High-grade dysplasia  | 21.082| <0.001  | 4.173 (2.268~7.678) | 0.38 (0.29~0.48)     | 0.88 (0.84~0.92)     | 0.56 (0.43~0.67)                  | 0.79 (0.74~0.84)                   |

*Four endoscopic findings and high grade dysplasia at forcep biopsies were proven to be independent risk factors for carcinoma transformation after endoscopic resection by logistic regression test.

**High grade dysplasia at forceps biopsy was revealed to be the most influential factor to predict carcinomatous transformation after endoscopic resection.

The positive predictive values of four endoscopic indicators ranged from 0.38 to 0.40, and the negative predictive values were in the range of 0.76 to 0.83.

DISCUSSION

We found that the concordance rate between the forceps biopsy samples and the post-resection specimens was 62.2% and that 27.2% of FBP adenomas were found to be carcinomas after resection, within the 6% to 47% range of previous reports. This discrepancy between forceps biopsy samples and post-resection specimens is likely unavoidable and an inevitable limitation of forceps biopsy, due to the small amount of tissue sampled.

In this investigation, which was based on white light endoscopic images, we found that some specimen features, including size of 15 mm or greater, depressed appearance, central concavity, and nodular surface, were useful for predicting carcinoma as a final diagnosis in FBP adenomas, regardless of histologic grades. Previous studies have suggested high-grade dysplasia as the exclusive predictive factor carcinoma as a final diagnosis, through Kim et al. found that depressed appearance is also predictive. One large scale study of 554 cases found that high-grade dysplasia, a biopsy number of more than three, size of no less than 2.0 cm, a morphologic type of depressed or yamada type IV, and a red or mixed-or-undetermined coloration were all predictive factors of carcinoma as a final diagnosis before resection. However, it is unclear whether these associations were generated by multivariate analysis, so the accuracy and validity of their findings is uncertain. In contrast to that study, we performed a logistic regression test to indentify independent endoscopic predictive factors for carcinoma as a final diagnosis.

One peculiar feature that we evaluated was the central concavity of the specimen (Fig. 1A), a feature distinct from depressed lesions with marginal elevation. One study reported previously that central concavity of FBP adenomas is highly suggestive of carcinoma. We adopted this indicator when we evaluated the malignant potential of elevated lesions and verified that central concavity is an independent predictive factor.

We also calculated the sensitivity, specificity, positive and negative predictive values, as well the $P$ values and Exp (B) for each predictive factors. The most sensitive indicator of carcinoma as a final diagnosis was size ≥ 15 mm, and the presence of high-grade dysplasia was the most specific predictor. Among endoscopic predictors, depressed appearance was most specific. Interestingly, the
spectrum positive predictive values of endoscopic factors fell within a relatively narrow range (0.38 to 0.40), as did negative predictive values (0.76 to 0.83). With these data, it is possible that the probability of carcinoma as a final diagnosis of a FBP adenoma with one of four specific endoscopic features is about 38% to 40%. The same rule also can be adjusted to the probability of sustaining adenoma as a final diagnosis based on negative predictive values.

The most influential endoscopic predictor was size, which had the highest Wald test score of 13.008. This result is corroborated by previous findings by others; however, pathologic underestimation for forceps-biopsy specimen can be suspected although the major reason must be focal carcinomatous change in adenoma.

There are several limitations to our study. The most important limitation could be selection bias. Although we included all consecutive cases over a set time period, there is still the possibility that selection bias could occur because this study was performed retrospectively in one hospital. Moreover, there are some patients who did not undergo endoscopic resection for FBP adenomas, not an infrequent occurrence in rural areas. Second, the endoscopic findings could be judged differently by endoscopists from other centers, although we regularly participate in many conferences discussing endoscopic features.

An additional large-scale prospective study must be performed in order to overcome these limitations.

In conclusion, we found four important endoscopic indicators that could function as feasible independent predictors of carcinoma as a final diagnosis in FBP adenomas: size ≥15 mm, depressed appearance or central concavity, and nodular surface. Our results suggest that it is needed to perform immediate endoscopic resection for FBP adenomas with these four endoscopic indicators to avoid missing optimal time for further evaluation and treatment.

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