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Non-adenomatous Dysplasia in Barrett's Esophagus; A Clinical, Pathologic and DNA Content Flow Cytometric Study

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Dysplasia; Barrett's esophagus; esophageal adenocarcinoma; aneuploidy; tetraploidy

Introduction

Patients with Barrett's esophagus (BE) are at increased risk for the development of esophageal adenocarcinoma (EA).^{2,3} EA evolves through a metaplasia, dysplasia, carcinoma sequence, although most patients with BE do not progress to EA during their lifetimes.⁵ At present, the morphologic identification of dysplasia in endoscopic mucosal biopsies is the standard method of detecting patients at increased risk for EA.²⁰ Traditionally, dysplasia is categorized as either low- or high-grade based on the degree of cytologic and/or architectural atypia of the epithelium.^{10,15} Atypical features include nuclear hyperchromasia and pleomorphism, nuclear stratification, increased mitoses, loss of nuclear polarity and mucin depletion. With higher grades of dysplasia, architectural abnormalities, such as crypt crowding and increased crypt branching, may be present as well.

In general, the features of dysplasia in BE resemble those seen in colonic adenomas because of the presence of elongated pencil-shaped nuclei with clumped chromatin and prominent nuclear stratification. As a result, this type of dysplasia has been referred to as "adenomatous" dysplasia anecdotally. However, rarely, dysplasia does not resemble the type seen in colonic

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adenomas, but instead is composed of crypts with a more prominent back-to-back gland pattern, containing cells that are more cuboidal in shape with high nuclear/cytoplasmic ratio, round to oval-shaped nuclei with an open chromatin pattern and prominent nucleoli. This type of dysplasia is not characterized by nuclear stratification typical of adenomatous dysplasia, and, as a result, has been termed “non-adenomatous” (NAD) or “foveolar” dysplasia anecdotally.¹² The histologic features have been noted, briefly, in previous reports.^{10,15} However, no specific clinical, pathologic or outcome study has been reported on this entity. Therefore, the aim of this study was to systematically evaluate the prevalence, clinical and pathologic features, and natural history, of a prospectively acquired cohort of high risk patients with BE and NAD who have been clinically followed with a standardized and rigorous endoscopic surveillance protocol.

Material and Methods

A. Patient cohort and study design

The Seattle Barrett’s Esophagus Study is an ongoing cohort study in which clinical, endoscopic, pathologic and DNA content flow cytometric data are evaluated prospectively. The Seattle Barrett’s Esophagus Study was approved by the Human Subjects Division of the University of Washington in 1983 and renewed annually thereafter with reciprocity from the Fred Hutchinson Cancer Research Center (FHCRC) Institutional Review Board from 1993 to 2001. Since 2001, the study has been approved by the FHCRC IRB with reciprocity from the University of Washington Human Subjects Division.

Endoscopic biopsy protocols used in the Seattle Barrett’s Esophagus Study have been published previously.⁶ Four quadrant biopsies for histology were taken every 1 cm (for high-risk patients with high-grade dysplasia or DNA content abnormalities) or every 2 cm (for low-risk patients without high-grade dysplasia or DNA content abnormalities) at intervals ranging from every 6 months (for high-risk patients) to 3 years, as described previously.¹⁶ Endoscopic biopsies from every 2-cm, for flow cytometry, were placed into media with 10% DMSO (dimethyl sulfoxide) within 15 seconds and held on ice until frozen and stored at -70C.

For this study, we analyzed 270 of the 309 patients in the cohort, prospectively, from July 2001 to February 2008. Thirty-nine patients without endoscopically visible BE or EA at their baseline endoscopy were excluded from the analysis. The 270 remaining BE patients were categorized as either “study” (ie. those with NAD) or “control” patients (ie. those without NAD). The two groups of patients were compared for their clinical, endoscopic, pathologic, natural history and DNA content flow cytometric data. All patients had metaplastic columnar epithelium, with goblet cells, in esophageal biopsies confirmed by evaluation of one of the authors (RDO) at the Brigham and Women’s Hospital, Boston, MA. Clinical features evaluated include gender, age at the time of diagnosis, and the length of BE as defined by the total cm of Barrett’s mucosa spanning the ora serrata and the distal end of the esophagus or lower esophageal sphincter (LES). The follow up interval was calculated as the length of time (in months) from the patient’s initial diagnosis of NAD for the study patients, and from the baseline biopsy in the control patients, to the time of the most recent follow-up endoscopy, or endoscopic mucosal resection (EMR).

B. Pathology Methods

Non-adenomatous dysplasia was defined by the presence of crypts with a back-to-back gland pattern, cuboidal-shaped cells with a high nuclear/cytoplasmic ratio, slight pleomorphism, round to oval-shaped nuclei, and, in many instances, prominent nucleoli (Figure 1). In contrast to adenomatous dysplasia, NAD does not show elongated pencil-shaped nuclei with clumped chromatin, nor stratification of the nuclei, features more typical of colonic adenomas (Figure

2). In addition, none of the NAD foci were associated with erosions, ulcers or active (neutrophilic) inflammation in the lamina propria or epithelium. Adenomatous dysplasia was categorized as either low- or high-grade according to previously published criteria.¹⁸ Esophageal adenocarcinoma was defined by the presence of neoplastic cells infiltrating the lamina propria and/or submucosa.

A total of 44 BE biopsies (range: 1-8) from 28 surveillance endoscopies (range: 1-4 endoscopies per patient) in the 18 study patients with NAD were evaluated for a wide variety of pathologic features including the distribution of dysplastic foci (focal = present in one biopsy, diffuse = present in $\geq$ one biopsy), location of crypt and/or surface epithelial involvement, cell type of the adjacent non-dysplastic epithelium (non-goblet versus goblet cell), relationship to the neo-squamocolumnar junction, and relationship to areas of conventional (adenomatous) dysplasia when present. Adenomatous dysplasia was assessed in NAD patient biopsies obtained from either the same, or subsequent, endoscopic procedures during the study period, and graded as either low- or high-grade.

C. Flow Cytometry Methods

Fresh frozen biopsies obtained from the endoscopic procedure from each of the study and control patients were evaluated prospectively for DNA content flow cytometry.^{14,16} Cell cycle analysis was performed on 71 BE biopsies from 13 of 18 study patients with NAD and 1,397 BE biopsies from 235 of 252 control patients. Tetraploidy and aneuploidy was defined as described previously.¹⁶ Flow cytometric data was not restricted to one biopsy per 2-cm level of esophagus.

D. Statistical Analysis

Statistical comparisons of clinical, histologic, and flow cytometric data for discrete counts were performed using Fischer's exact test. Non-paired t-test was used for comparison of means. The p-value of <0.05 was considered as the threshold for statistical significance. All of the analyses were performed with Statistical Analysis System (SAS) software (version 9.0; SAS institute, Carrey, North Carolina, NC).

Results

1. Clinical data

The clinical and endoscopic features of the study patients with NAD and controls are summarized in Table 1. NAD was observed in 18 (6.7%) of 270 BE patients evaluated prospectively. The 252 controls were further subdivided into patients with or without conventional adenomatous dysplasia for further comparison with the NAD study group. At their baseline endoscopy, the control group included 228 of 252 (91%) with metaplasia or indefinite for dysplasia and 24 (10%) with adenomatous dysplasia (13 low-grade and 11 high-grade). Seventeen of the 18 (94%) NAD patients also had associated adenomatous dysplasia (four low-grade and 13 high-grade). The study group with NAD consisted of 17 males and one female of mean age 66.7 years (range: 44-80 years). The control patients without NAD consisted of 206 males and 46 females with a mean age of 64 (range: 33-94 years). The mean length of BE in the NAD patients was 3.9 cm (range: 0.1-7.0 cm) compared to a mean of 6.0 cm (range: 0.1-15 cm) in the subgroup of control patients with adenomatous dysplasia ($p=0.03$). Otherwise, there were no significant differences in the clinical or endoscopic features between the study patients with NAD compared to the control patients in total, or with the subgroups of controls. Study patients were followed for a mean of 52 months (range: 10-78), which was similar to the mean of 46 months (range: 1-80) for the control group.

2. Pathology results

Of the 18 study patients, NAD was documented in 44 separate mucosal biopsies (range: 1-8) from 28 surveillance endoscopies (range: 1-4 endoscopies per patient) (Figure 1). A summary of the pathologic characteristics of NAD in the 18 study cases is provided in Table 2. In 13 patients, NAD was detected in one biopsy fragment and in five, it was detected in multiple (> one) biopsies from different levels of the esophagus. NAD showed goblet cell differentiation in four cases, and mucinous differentiation in three. Foci of NAD most commonly involved both the crypts and surface epithelium (full crypt involvement), but involved only the bases of the crypts in 4 biopsies (8.5%). NAD was more frequently associated with metaplastic epithelium with goblet cells (62%) compared to non-goblet epithelium (38%). It was most commonly found adjacent to the neo-squamocolumnar junction (55%). None of the NAD foci were associated with active inflammation or ulceration.

Most 17/18 (94%) patients with NAD also had foci of conventional adenomatous dysplasia in the same endoscopic procedure in which the NAD was initially discovered (Figure 2). Of the 17 NAD patients with conventional adenomatous dysplasia, four had associated low-grade and 13 had associated high-grade as the highest degree of dysplasia other than NAD.

3. DNA content flow cytometric results

DNA content flow cytometric data was available for 13 (72%) of the 18 NAD patients within six months of the endoscopy and for 235 (93%) of the 252 controls at their baseline endoscopy. The flow cytometric data is summarized in Table 3. In five of 13 (38%) NAD patients we detected either tetraploidy or aneuploidy, or both, in biopsies obtained at endoscopy. In three patients with NAD (23%), we detected tetraploidy in two and aneuploidy in one. However, two (15%) patients with NAD had both tetraploidy and aneuploidy detected at endoscopy. In the control group, we detected a significantly lower proportion of DNA content flow cytometric abnormalities of tetraploidy and/or aneuploidy, in 25 (11%) of patients ($p<0.05$). Twenty-one (8%) patients had either tetraploidy or aneuploidy detected at endoscopy, and four (2%) had both tetraploidy and aneuploidy detected. When analyzed and compared to the control subgroups, a significant increase in flow cytometric abnormalities were observed in the NAD group compared to the controls with metaplasia/indefinite for dysplasia group ($p<0.05$). However, no significant differences were observed by flow cytometry between the study patients with NAD and the control patients with conventional adenomatous dysplasia, or between the study patients and each individual control group with either low- or high-grade adenomatous dysplasia.

4. Follow up data

Table 4 summarizes the follow up data for the BE patients evaluated in this study. The 18 study patients with NAD underwent 56 endoscopies during the study period (range: 1-5 per patient). The 252 control BE patients without NAD underwent 846 endoscopies during the same time period (range: 1-13).

Of the 18 patients with NAD, 1 (5%) showed no evidence of dysplasia upon follow up, 14 (78%) showed conventional adenomatous dysplasia and 3 (17%) developed (EA). Seventeen of 18 (94%) had concurrent conventional adenomatous dysplasia. Three of 4 (75%) NAD patients with concurrent low-grade adenomatous dysplasia progressed from the initial NAD observation to high-grade adenomatous dysplasia over a mean of 23.7 months and one progressed to EA at 11.6 months. Two (15%) of the 13 NAD patients with concurrent conventional adenomatous high-grade dysplasia progressed to EA over 37.1 months. The follow-up of the four NAD patients with concurrent low-grade adenomatous dysplasia was similar to the 13 NAD patients with associated conventional high-grade dysplasia in which 11

(85%) showed further foci of high-grade adenomatous dysplasia and two (15%) developed EA upon follow up.

Separate follow up comparisons were performed on the study patients with NAD and the control patients with either conventional low- or high-grade adenomatous dysplasia. As noted in Table 4, the development of conventional adenomatous dysplasia and EA was significantly higher in patients with NAD (17%) compared to the control group (5%) in total, and when compared to the subgroup of control patients with metaplasia or indefinite for dysplasia in their baseline biopsies ($p<0.05$). However, no differences were noted in the frequency of development of high-grade adenomatous dysplasia or EA between the patients with NAD and the control patients with adenomatous dysplasia in their baseline biopsies. Of the control patients with adenomatous dysplasia, 13 (54%) and five (21%) ultimately developed these changes within a mean of 19.8 and 18.0 months, respectively. Further, the prevalence rate and follow up time to EA detection was similar between the study patients with NAD compared to the control patients without NAD, but with either conventional low- or high-grade adenomatous dysplasia.

Discussion

Most cases of dysplasia arising in BE are characterized by a proliferation of cells with elongated pencil-shaped hyperchromatic nuclei with clumped chromatin, and stratification, features that resemble the appearance of dysplastic cells in colonic adenomas.^{10,15} As a result, this has been referred to, rather anecdotally, as “adenomatous” dysplasia. However, rarely, BE-related dysplasia may be composed of cells with cuboidal, instead of elongated, shape, round to oval nuclei with an open chromatin pattern and prominent nucleoli, a high nuclear/cytoplasmic ratio, but without nuclear stratification characteristic of adenomatous dysplasia. Unfortunately, neither the association of the two types of dysplasia nor the clinical significance of NAD has been investigated previously. Thus, the purpose of this study was to evaluate the clinical, morphologic, DNA content flow cytometric abnormalities, and, particularly, the natural history of patients with NAD.

In this study, the clinical, pathologic, DNA content flow cytometric and follow-up findings of 18 BE patients with at least 1 focus of NAD documented in endoscopic surveillance mucosal biopsies of the esophagus were evaluated and compared to a control group of 252 BE patients without NAD. In addition, in order to compare and contrast the features of patients with NAD to the controls with adenomatous dysplasia, separate analyses were performed between the study patients with NAD and the subgroup of control patients with adenomatous dysplasia, either low- or high-grade. The prevalence rate of NAD in our high risk BE cohort was 6.7%. Non-adenomatous dysplasia occurred in goblet rich epithelium in 62% of foci, and non-goblet epithelium in 38% of foci. One of the striking findings of our study was the close association between NAD and conventional adenomatous dysplasia; 94% of patients (17/18) with NAD also had conventional adenomatous dysplasia. Of the foci of associated adenomatous dysplasia, 77% were high-grade and 23% were low-grade. Thirty-eight percent of NAD patients showed at least one DNA content flow abnormality (tetraploidy and/or aneuploidy) in biopsies obtained at the same endoscopic procedure and although this value was significantly higher than control patients without dysplasia or with indefinite for dysplasia, no significant differences were observed compared to control patients with adenomatous dysplasia, either low- or high-grade. Upon follow-up, all study patients, except one (95%), developed further foci of adenomatous high-grade dysplasia (78%) or invasive carcinoma (17%). Only one (7%) of 14 patients developed further foci of NAD. Progression to EA in patients with NAD and associated adenomatous dysplasia was similar to control patients with adenomatous dysplasia. The only statistically significant results occurred when a comparison was made between NAD patients as a group with the subset of controls without dysplasia. Based on these data, we conclude that

NAD is a high-grade histologic variant of intraepithelial neoplasia and should be managed similarly to patients with conventional adenomatous high-grade dysplasia.

This is the first study to objectively evaluate the biological characteristics of NAD. In the original BE-associated dysplasia interobserver study by Reid et al in 1988, which was based on a newly conceived classification of dysplasia into negative, indefinite, and positive (either low- or high-grade), NAD was not specifically evaluated.¹⁵ In fact, the number of cases of dysplasia that had adenomatous-like nuclear stratification versus non-stratified nuclei was not documented. The authors of that study commented that “although nuclear stratification was found frequently in association with dysplasia, stratification alone was insufficient to make the diagnosis (of dysplasia)”. Interestingly, the case illustrated in Figure 13 of that study shows cytologic features similar to the NAD cases evaluated in our current study. In the Reid study, that case was felt to represent low-grade dysplasia by half of the observers and high-grade dysplasia by the other half. The lack of nuclear stratification led the observers to conclude that the cytologic features were low-grade, but the observers who considered the histologic features as indicative of high-grade, did so on the basis of architectural distortion, such as the presence of a compact back-to-back gland arrangement. In fact, the authors noted that some morphologists were reluctant to assign a diagnosis of high-grade dysplasia in what they perceived to be an absence of both architectural and cytologic abnormalities. However, others felt that either one or the other of these features alone was sufficient to render a diagnosis of high-grade dysplasia.

In the only other study that evaluated specific histologic features of dysplasia in BE, Montgomery et al formulated more stringent criteria for dysplasia in BE and tested the reproducibility of 125 cases with 12 GI pathologists.¹⁰ In contrast to the results by Reid et al, in the study by Montgomery et al, high-grade dysplasia was determined to be present if either high-grade cytologic changes or significant architectural distortion (characterized by little or no lamina propria between the crypts) were identified in biopsy specimens. However, in that study, distinction between adenomatous and non-adenomatous features was not specifically addressed. In fact, the criteria for dysplasia in that study included “stratification often extending from the epithelial basement membrane to the luminal surface.” However, the authors did note that “prominent irregular nuclei with irregularly clumped chromatin and irregular nucleoli are a feature of high-grade dysplasia.” These are features reminiscent of NAD in our study. Interestingly, Figure 10 in the Montgomery paper, representing a case of dysplasia fixed in Hollande’s fixative, shows focal changes of NAD characterized by cuboidal, instead of elongated, cells, with round-oval shaped nuclei and lack of nuclear stratification. In that study, it was felt that this focus of dysplasia could not be graded accurately. Of the 24 readings, 11 observers diagnosed low-grade dysplasia, 10 high-grade dysplasia, and 3 intramucosal adenocarcinoma. Similarly, in a follow-up study from the same group of investigators based on the cases from the initial diagnostic variability study, distinction between adenomatous dysplasia and NAD was not made with regard to outcome.¹¹

Most forms of dysplasia in the gastrointestinal tract, such as that which occurs in the stomach or colon, are composed of columnar cells with elongated pencil-shaped nuclei with stratification.^{13,18} However, non-adenomatous histologic variants of dysplasia have been described in other organs, such as the stomach.¹³ For instance, one type of gastric dysplasia is composed of glands of variable size and shape, and cells that are cuboidal or low-columnar with clear eosinophilic cytoplasm and round-oval shaped vesicular nuclei with nucleoli. This type of dysplasia has been referred to at “Type 2,” “hyperplastic” or “foveolar” dysplasia.¹³ The nuclear features of gastric foveolar dysplasia are reminiscent of NAD in BE. Although no outcome studies have been performed on foveolar dysplasia of the stomach, some authors have noted an association with poorly-differentiated adenocarcinoma of the intestinal type, and non-metaplastic foveolar, or pylori gland-type, gastric epithelium. Interestingly, 38% of our patients

developed NAD within non-goblet epithelium. Although, historically, dysplasia in BE has been noted to develop predominantly in intestinalized epithelium (ie. epithelium with goblet cells), a recent study by Takubo et al showed that 70% of 141 cases of primary small (<2 cm) adenocarcinomas of the esophagus were situated adjacent to cardia or fundic-type mucosa rather than intestinal-type mucosa with goblet cells.¹⁹

Previous studies by our group, as well as others, have shown that neoplastic progression in BE arises as a result of acquired genetic instability, and subsequent evolution of clonal populations with accumulated genetic lesions.^{1,4,7-9,14,16,17} DNA content flow cytometry to identify patients with tetraploidy or aneuploidy has been shown to be an effective adjunct to histology in helping to stratify patients with BE into low- and high-risk subsets. For instance, a DNA content flow cytometric study by Reid and colleagues in 2000 showed that patients without detectable DNA content abnormalities in their baseline biopsies had a 0% incidence of adenocarcinoma compared to a 28% incidence rate in BE patients with either aneuploidy or increased 4N fraction (tetraploidy).¹⁶ In our current study, 38% of patients with NAD had increased tetraploidy or aneuploidy which was statistically similar to the control patients with adenomatous dysplasia. Thus, based on this data, we do not feel that the presence of DNA content flow abnormalities, and specifically tetraploidy or aneuploidy, are associated with the development of NAD and probably reflect a general underlying instability of the epithelium in BE.

One of the limitations of this study is based on the fact that the Seattle Barrett's esophagus cohort is a high risk population of patients with BE, and, thus, may not necessarily be representative of the general population. Thus, it is probable that the prevalence rate of NAD in our study, and of dysplasia in general, is higher in this cohort compared to the general population. Another difficulty of interpretation of our data is that the majority of patients with NAD (94%) in our study also had conventional adenomatous dysplasia in other biopsies from the same endoscopic procedure. Therefore, it is difficult to distinguish the contribution of adenomatous versus non-adenomatous dysplasia when evaluating flow cytometric abnormalities or clinical follow up. Flow cytometric data and outcome data were statistically similar in the study and control groups, and a much larger study would be required to determine the independent significance of NAD and adenomatous dysplasia with regard to patient management.

In summary, we described the clinical, pathologic, DNA content flow cytometric, and outcome data of a cohort of high risk BE patients who had NAD in their esophageal mucosal biopsies. NAD is a high-grade histologic variant of intraepithelial neoplasia, is often episodic in nature, and shows a high association with conventional adenomatous high-grade dysplasia. Further molecular and prospective studies should be done in order to characterize the molecular phenotype that leads to NAD and the potential long-term sequela of patients with this type of dysplasia.

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Figure 1.

A. Medium power view of a focus of NAD in a patient with BE. The epithelium shows a back-to-back arrangement of crypts containing basally located, round, oval-shaped nuclei, open chromatin pattern, and prominent nucleoli. Loss of cell polarity is minimal, except for focally at the surface epithelium. There is no significant nuclear stratification. B. High power view showing the nuclear features which consist of round to oval-shaped irregular nuclei, peripheral condensation of chromatin, open chromatin pattern and prominent nucleoli. C. Another BE patient with NAD showing less of a back-to-back crypt pattern and slightly more chronic inflammation in the lamina propria. In this particular biopsy, the bases of the crypts show a slight degree of crypt branching. D. High power view of the same area showing the characteristic nuclear features of NAD.

Figure 2.

Focus of conventional adenomatous dysplasia (high-grade) in a patient with NAD. In contrast to NAD, conventional adenomatous dysplasia shows enlarged hyperchromatic pencil-shaped nuclei with clumped chromatin and prominent stratification. In this case, full thickness nuclear stratification and significant loss of cell polarity warrant a diagnosis of high-grade conventional adenomatous dysplasia.

Table 1

Clinical Features of Study Patients and Controls

Patient Group	N	Male/Female ratio	Mean Age (range)	Feature Mean length of Barrett's in cm (range)	Mean follow-up (months)
Non-adenomatous Dysplasia	18	17/1	66.7(44-80)	3.9(0.1-7.0)	52
Controls	252	206/46	64(33-94)	5.0(0-17)	46
Metaplasia/Indefinite	228	186/42	64(41-94)	4.9(0-17)	46
Adenomatous dysplasia	24	20/4	63(35-88)	6.0(0-15) ^{*I}	44
Low-grade	13/24	11/2	65(41-80)	5.8(0-11)	48
High-grade	11/24	9/2	60(35-88)	7.0(1-15)	36

^{*I} p = 0.03 Non-adenomatous dysplasia (n=18) vs. adenomatous dysplasia (n=24)

Table 2**Histologic Features of 18 Study Patients with Non-adenomatous Dysplasia**

Feature	Prevalence
Non-adenomatous dysplasia involvement of crypts and surface	43/47 (91.5%)
Non-adenomatous dysplasia involvement of crypts only	4/47(8.5%)
Associated with non-goblet epithelium	18/47(38%)
Associated with goblet cell epithelium	29/47(62%)
Adjacent to squamous mucosa	24/47(51%)
Beneath squamous mucosa	2/47(4%)
No association with squamous mucosa	21/47(45%)
Significant architectural distortion	8/47(17%) ^{*I}
Adenomatous dysplasia on current biopsy	17/18 (94%)
Low-grade	4/17(25%)
High-grade	13/17(76%)

^{*I} 8 foci from 2 patients

Table 3
DNA Content Flow Cytometric Results of Study and Control Patients

Patient Group	N	Flow Abnormality		
		Tetraploidy or Aneuploidy (one abnormality)	Tetraploidy and Aneuploidy (two abnormalities)	Tetraploidy and/or Aneuploidy (one, two or both abnormalities)
Non-adenomatous Dysplasia	13	3(23%)	2(15%)	5(38%)
Controls	235	21(8%) ^{*2}	4(2%) ^{*1}	25(11%) ^{*1}
Metaplasia/Indefinite	218	17(7%) ^{*2}	2(0.9%) ^{*1}	19(8%) ^{*1}
Adenomatous dysplasia	17	4(24%)	2(12%)	6(35%)
Low-grade	9	3(33%)	1(11%)	4(44%)
High-grade	8	1(13%)	1(13%)	2(25%)

^{*1}
 $p < 0.05$ vs Non-adenomatous dysplasia

^{*2}
 $p < 0.09$ vs Non-adenomatous dysplasia

Table 4
Progression Status of Study and Control Patients Upon Follow-up

Patient Group	N	Maximum Diagnosis in Follow-up			EA
		Metaplasia/Indefinite	Dysplasia Grade		
			Low	High	
Non-adenomatous Dysplasia	18	1 (6%)	0 (0%)	14 (78%)	3 (17%)
Concurrent Low-grade ^{*2}	4			3 (75%)	1 (25%)
Concurrent High-grade ^{*2}	13			11 (84%)	2 (15%)
Controls	252		41 (16%)	18 (7%)	12 (5%)
Metaplasia/Indefinite	228	181 (79%)	35 (15%)	5 (2%)	7 (3%) ^{*1}
Adenomatous Dysplasia	24	-	6 (25%)	13 (54%)	5 (21%)
Low-grade	13	-	6 (46%)	4 (31%)	3 (23%)
High-grade	11	-	-	9 (82%)	2 (18%)

^{*1} $p < 0.05$ vs. Non-adenomatous dysplasia
^{*2} refers to concurrent adenomatous dysplasia