

## EARLY GASTRIC NEOPLASMS: DIAGNOSES AND IMPLICATIONS

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Despite a marked decline in incidence in the West and some decrease in the East, gastric cancer remains a significant cause of morbidity and cancer related deaths worldwide. The prevalence of gastric cancer is closely related to prevalence of *Helicobacter pylori* infection and shows wide geographic variation. Subsequent chronic gastritis, atrophy, and intestinal metaplasia are lesions that confer a high risk for the development of gastric cancer, while gastric dysplasia, the penultimate stage of the carcinogenetic cascade, is a direct neoplastic precursor lesion.<sup>2, 4, 14-16, 18, 22, 36, 41, 60, 64</sup> Evidence for gastric dysplasia as a direct precursor of adenocarcinoma stems from observational studies reporting high-grade dysplasia (HGD) in close proximity to 40-100% of early gastric cancers and 5-80% of advanced adenocarcinomas.<sup>48, 61, 95</sup> Moreover, dysplasia is also a marker of increased risk for cancer elsewhere in the gastric mucosa.

As with gastric cancer, the prevalence of dysplasia shows wide geographic variations. The difference is likely related to variations in the genetic makeup of the population, as well as variations in environmental factors, such as the prevalence of *Helicobacter pylori* infection (and subtype) and the age at which the infection is acquired.<sup>2, 6, 11, 14-16, 18, 22, 25, 51, 60, 64, 79, 95</sup> The frequency of dysplasia also varies with the underlying etiology. For instance, prevalence rates of up to 40% have been reported in patients with pernicious anemia but the disease confers only a moderate increase in risk of developing gastric cancer.<sup>3, 6, 33, 94</sup> In the setting of familial adenomatous polyposis (FAP), flat or polypoid dysplasias, typically antral in location, are frequently multiple and may be seen in 2-50% of patients.<sup>7, 8, 10, 21, 31, 38, 74, 75, 80, 82, 86, 87</sup> Patients with a gastric remnant status post gastrectomy, Menetrier's disease, or Peutz-Jegher's syndrome also are at increased risk.<sup>5, 44, 81, 89</sup>

## **Classification of Gastric Epithelial Dysplasia**

The classification of dysplastic lesions has been controversial, with various diagnostic criteria used across the world. Japanese authors refer to these as borderline (Group 3 or 4) lesions, while the terms gastric adenoma (for raised lesions) and gastric dysplasia (for flat/depressed lesions) have been widely used in the Western literature.<sup>32, 67, 77</sup>

Earlier guidelines for the diagnosis and grading of gastric dysplasia embraced a three-tiered system of mild, moderate and severe dysplasia. As in any segment of the gastrointestinal tract, dysplasia was defined as "unequivocally neoplastic epithelium that may be associated with or give rise to invasive adenocarcinoma."<sup>54, 57, 66</sup> Later schemes have proposed a two-tiered system of low- and high-grade dysplasia,<sup>48, 69, 70, 78</sup> which has proven to be more reproducible and provides a clinically meaningful risk stratification.<sup>32, 47</sup> The WHO recommends the terminology of non-invasive low-grade and high-grade intraepithelial neoplasia, and defines carcinoma as invasion into the lamina propria or beyond.<sup>34</sup> However, the terminology of adenoma/dysplasia is widely entrenched, and continues to be used, particularly in North America.

A significant debate has occurred over differentiating adenocarcinoma from high-grade dysplasia. Furthermore, the complexity of cyto-architectural features has been considered to be of paramount importance for the diagnosis of carcinoma in Japan, while breach of the basement membrane and invasion into the lamina propria has been considered the *sine qua non* of malignancy and hence a prerequisite for the diagnosis of cancer in the West.<sup>47, 76</sup> As an attempt to bridge differences, the Vienna classification was developed as a consensus between Western and Asian investigators.<sup>78</sup> This consensus view takes into account the discrepancies in the reporting of dysplasia between Japanese and Western pathologists. For example, non-invasive intramucosal neoplastic lesions with high-grade cellular and/or architectural atypia are classified as "intramucosal carcinoma" in Japan, whereas similar lesions are diagnosed as high-grade dysplasia by most Western pathologists. In the Vienna classification, high-grade lesions without invasion of the lamina propria and adenocarcinomas with invasion confined to the lamina propria, are now placed into a single diagnostic category, a rationale supported by current endoscopic management.

### **Phenotypic variants of gastric dysplasia**

Most examples of dysplasia have an "intestinal" phenotype, i.e., resembling colonic adenomas. These lesions are commonly referred to as *adenomatous* (or type I) *dysplasia*. The histologic characteristics include crowded glands lined by tall columnar cells with pencillate, overlapping, and hyperchromatic nuclei which show pseudostratification and inconspicuous nucleoli.<sup>42</sup> Other less common histologic variants include *foveolar* (type II or non-adenomatous) dysplasia and *pyloric* type dysplasia.<sup>42</sup> The distinctive feature of Type II dysplasia is the presence of glands lined by either low cuboidal or columnar epithelium with pale-clear cytoplasm, round-oval, vesicular nuclei and variably prominent nucleoli. Although prior studies have suggested that this form of dysplasia is almost always low-grade,<sup>1</sup> more recent studies indicate that Type II dysplasia may be associated with distinct clinico-pathological characteristics and is more often high-grade when evaluated in a high-risk population.<sup>63</sup> Some authors have indicated that Type II dysplasia is more commonly associated with poorly-differentiated adenocarcinoma.<sup>42, 56, 58</sup>

*Pyloric* type dysplasia is a recently recognized type of dysplasia. Frequently observed in the body fundus, it is commonly seen in the older population. Some series indicate that it is commonly shows high grade dysplasia.<sup>13</sup>

*Tubule neck* (or globoid) dysplasia is exceedingly rare and is believed to be a precursor of diffuse-type gastric carcinoma.<sup>30</sup> It occurs in non-metaplastic gastric epithelium and appears as enlarged, clear cells occupying the gland neck region and confined within the basement membrane.

In the setting of inherited germline E-cadherin/CDH1 gene mutation, prophylactic gastrectomies have shown examples of "signet ring cell carcinoma in situ," often with a "pagetoid" spread between the gastric foveolar and glandular epithelium within the basement membrane.<sup>12, 50</sup> These changes are often multifocal and have a predilection for the proximal stomach and the body-antral transitional zone.

### **Grading of gastric dysplasia**

The two-tiered scheme of low and high grade is widely used in all classification schemes. Practically, gastric biopsies need to be categorized into one of several categories: negative for dysplasia, indefinite for dysplasia, low grade dysplasia/adenoma, high grade dysplasia/adenoma, intramucosal carcinoma or an invasive adenocarcinoma.

#### *Indefinite for dysplasia*

There are cases for which one cannot establish a diagnosis with certainty. Commonly it means differentiating between reactive epithelial changes and dysplasia. It should be seen as a provisional designation that emphasizes the need to follow up the patient and to obtain additional biopsies. Alternatively, it should not be used as a wastebasket term for all cases with reactive atypia which are obviously in response to inflammatory or direct mucosal injury. Clues to the reactive nature of the epithelial changes includes the presence of vascular congestion and a gradual rather than abrupt transition between the atypical and adjacent normal cells.<sup>54, 66</sup>

#### *Low-grade dysplasia (Adenoma; Non-invasive intraepithelial neoplasia-low grade)*

We used the term "adenoma" for elevated mucosal lesions and low grade dysplasia for flat lesions that show minimal architectural disarray and cytological atypia.<sup>32, 47, 54, 66, 95</sup> As mentioned earlier, in most cases, the morphological appearance is reminiscent of colonic adenomas and the lesions often occur in a background of intestinal metaplasia. The criteria for separating Type II dysplasia into low and high grade categories are not well established. The presence of gastric foveolar type epithelium with elongated, hyperchromatic nuclei that show some degree of pseudostratification is categorized as low-grade Type II dysplasia. Although a designation of low-grade implies a comparatively reduced risk of malignant transformation, it must be recognized that low-grade dysplasia occurring in a background of extensive intestinal metaplasia may be associated with a higher risk of malignancy.<sup>71</sup>

*High-grade dysplasia (Adenoma with high-grade dysplasia; Non-invasive intraepithelial neoplasia-high grade)*

Marked cytological atypia or architectural complexity deserve a diagnosis of high-grade dysplasia. High grade dysplastic glands are commonly lined by rounded, pleomorphic nuclei that show prominent nucleoli and loss of polarity. Marked irregularities of the nuclear membrane and clumping of chromatin are also features often associated with high grade dysplasia. However, marked glandular crowding, budding, and intra-luminal bridges should raise the question of early gastric cancer. Typical or atypical mitoses may be present in either low grade or high grade dysplasia, but are more often and more easily discernible in the latter category.<sup>32, 47, 69</sup>

*Intramucosal adenocarcinoma*

The controversy and disparity in literature regarding separation of "dysplasia" from "carcinoma" has already been alluded to above. The current approach to this problem is based on two facts: 1) "invasion," particularly when limited to the lamina propria, is difficult to identify on routine histology, and 2) intramucosal adenocarcinomas have a less than 10% risk of nodal metastases<sup>24</sup> and neoplastic lesions with invasion of the lamina propria but confined to the mucosa are, therefore, amenable to a conservative approach through endoscopic resection. Currently, lesions which show marked architectural atypia in the form of fused glandular pattern, cribriforming or intra-luminal necrosis, as well as those that show definite evidence of invasion into the lamina propria in the form of single cells or small clusters of cells, are categorized as intramucosal adenocarcinoma.

**Characteristics of intramucosal of adenocarcinomas**

Intramucosal adenocarcinoma belong to the category of early gastric cancers (EGC), which are defined as invasive adenocarcinomas confined to the mucosa or submucosa, whether lymph node metastasis is present or not.<sup>29, 49</sup> In Western series, EGCs represent between 15% and 21% of all newly diagnosed cancers, while in Japan, they account for over 50% of the cases.<sup>23, 28, 37, 83</sup> The higher prevalence of gastric cancer, a more liberal use of upper endoscopy, perhaps a better technique including chromoendoscopy, and a difference in diagnostic criteria may explain the difference.

Most EGCs are small, measuring between 2 cm and 5 cm and localized on the lesser curvature and around the angulus.<sup>49, 55</sup> Multiple tumors are seen in 3% to 13% of the patients, and are associated with a worse prognosis.<sup>23, 53</sup>

The Paris classification divides EGCs into 3 types based on the endoscopic macroscopic appearance (figure 2): Protruded (type I), superficial (type II), and excavated (type III).<sup>40</sup> Type II is further subdivided into IIa (elevated type), IIb (flat type), and IIc (depressed type). Superficial (type II) EGCs account for about 80% of the cases, with type IIc being the most common subtype.<sup>90</sup> Type IIb accounts for 58% of small tumors measuring less than 5 mm.<sup>45</sup> Notably, this endoscopic classification has shown to be a good indicator of the risk for nodal metastasis, reportedly low in type Ia or IIa EGC.<sup>19</sup>

The majority of EGCs are well differentiated glandular carcinomas. Tubular and papillary variants represent 52% and 37% of cases, respectively, and can be difficult to differentiate from dysplasia (see above). Signet ring cell carcinoma and poorly differentiated carcinoma represent 26% and 14% of the cases, and are usually depressed or ulcerated (types IIc and III).<sup>23, 49, 90</sup> Diffuse type EGCs tend to have a greater depth of invasion.<sup>19</sup>

### **Progression and outcome of early gastric neoplasms**

#### *A) Low –grade dysplasia*

Although assessing regression of low-grade dysplasia is difficult because of sampling issues and inter-observer variation in the diagnosis, it has been reported in 38-75%, while persistence is seen in 19-50% of cases.<sup>6, 9, 46</sup>

Historical data have reported progression to adenocarcinoma in 0-23% of patients with LGD within a span of 1-4 years, but recent studies indicated a lower risk of progression (0-9%), while there is a significant risk of malignant transformation associated in high-grade (10-100%).<sup>68, 91</sup>

### B) *High-grade dysplasia*

This diagnosis is more ominous, since HGD has been noted to persist in 14-58% of the cases and to progress to cancer in 60-85% of patients over a median interval of 4-48 months.<sup>20, 27, 43, 46, 70, 73, 91</sup> Regression, though, also has been reported, and varies from 0-16%.

### C) *Intramucosal adenocarcinoma*

In a series of patients diagnosed with EGC and followed without surgery, 63% of the tumors progressed to advanced carcinomas over a span of 6 to 88 months.<sup>84</sup> However, when resected, the prognosis of EGCs is excellent, with a five-year survival rate greater than 90% in most series.<sup>17, 23, 26, 39, 83</sup> The size and depth of invasion are the two major prognostic indicators, with the larger the diameter, the greater the risk of submucosal infiltration.<sup>28, 52, 93</sup> Notably, the risk of invasion should not be overlooked even in very small tumors. In one series, 15.5% of 3-5 mm EGCs invaded the submucosa.<sup>62</sup> Even for intramucosal EGCs, lymph node metastases have been reported in up to 7% of cases. However, the five-year survival remains close to 100%.<sup>23, 52, 93</sup> For EGCs extending into the submucosa, the rate of lymph node metastases is between 8% and 25%, and the five-year survival is 80% to 90%.<sup>23, 93</sup>

## **Management of early gastric neoplasms**

Given the demonstrated low rate of malignant transformation of low grade dysplasia and the development of newer endoscopic imaging techniques, such as chromoendoscopy, annual endoscopic surveillance with re-biopsy is typically performed and surgical resection is not necessary.<sup>72, 88</sup> Similarly, a diagnosis of indefinite for dysplasia should also prompt endoscopic surveillance and biopsy.

Although a diagnosis of high-grade dysplasia in years past was the indication for surgery, nowadays, this diagnosis as well as a diagnosis of intramucosal adenocarcinoma (provided deep submucosal invasion is ruled out with certainty with endoscopic ultrasound) will be managed endoscopically since *endoscopic mucosal resection* and *submucosal dissection* offer definitive therapy.

Endoscopic mucosal resection has rapidly become the treatment of choice in association with endoscopic ultrasound for staging. The primary criteria of EGC amenable to EMR are elevated lesions less than 2 cm in size, depressed lesions less than 1 cm in size without ulceration, and the absence of lymph node metastasis. Endoscopic submucosal dissection (ESD) is a more recent method developed in order to increase the en bloc and R0 resection rate, especially for lesions larger than 20 mm in diameter. Drawbacks of endoscopic submucosal dissection include the fact that it is technically a substantially more difficult procedure and that it is associated with a higher perforation rate.<sup>35, 59, 65, 92</sup> Finally, the eradication of *H. pylori* improves prognosis of patients with early neoplasms. In a study of 132 patients with EGC who underwent EMR, no new cases of gastric cancer were observed after resection when *H. pylori* was eradicated; in contrast, 13.5% of untreated patients had new early-stage intestinal-type gastric cancer.<sup>85</sup>

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