Chapter 5
Pathology of Gastric Cancer

Takashi Yao and Ryo Wada

Abstract Early detection and accurate diagnosis have strong impacts on cancer care; therefore, pathological diagnosis of biopsy specimen is important. It is too late that the lesion is followed up until the carcinoma invades the submucosa or more. For the better quality of life (QOL) of patients, carcinomas should be endoscopically diagnosed and resected before metastasis. To achieve correct histological diagnosis on early-stage gastric carcinomas by biopsy specimen, it is necessary to understand the difference in histological diagnosis between Japanese and Western pathologists and learn the characteristic histological features of noninvasive well-differentiated adenocarcinomas, especially those of low-grade atypia. In addition, for selecting the suitable therapy, it is also necessary to know the clinicopathological features of special types of gastric carcinomas and how to correctly perform a histological evaluation of endoscopically resected specimens.

Keywords Gastric cancer · Histological diagnosis · Adenocarcinoma with enteroblastic differentiation · Adenocarcinoma of fundic gland type · Endoscopic curative resection

5.1 Differences in Histological Diagnosis between Japanese and Western Pathologists

It is well known that there are discrepancies in the diagnosis of gastrointestinal neoplasia between Japanese and Western pathologists [1–6]. In Western countries, the most reliable finding for the diagnosis of carcinoma is the presence of stromal

T. Yao (✉)
Department of Human Pathology, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan
e-mail: tyao@juntendo.ac.jp

R. Wada
Department of Pathology, Juntendo University Shizuoka Hospital, Izunokuni, Shizuoka, Japan

A. Shiotani (ed.), *Gastric Cancer*, https://doi.org/10.1007/978-981-13-1120-8_5

invasion (desmoplastic reaction). Accordingly, noninvasive epithelial neoplasia is classified into low-grade dysplasia (LGD) and high-grade dysplasia (HGD) subtypes, by degree of cytological atypia. In contrast, in Japan the diagnosis of carcinoma is made by the combination of cytological and architectural abnormalities, irrespective of stromal invasion. Accordingly, noninvasive epithelial neoplasia is classified into adenoma and adenocarcinoma by cytological features.

In Japan, the five-tiered group classification is widely used for the histological diagnosis of endoscopic biopsy specimens. The updated group classification [7] is similar to the Vienna classification [3]; however, these two classifications are partly different. Between the two classifications, there is no difference between Group 1 and Category 1 (non-neoplasia) and Group 2 and Category 2 (indefinite for neoplasia), and the comparisons between Groups/Categories 3, 4, and 5 between the two classifications are demonstrated in Table 5.1.

In the Vienna classification system, the diagnoses of high-grade adenoma/HGD, noninvasive carcinoma, and suspicious invasive carcinoma are clustered into one category (Category 4), termed as noninvasive high-grade neoplasia. This category is defined as neoplasia with cytological and architectural features of carcinoma but without evidence of stromal invasion. Utilization of the Vienna classification system has improved the percentage of agreement during diagnoses [3, 4]. The different terms, HGD and intramucosal carcinoma, can be explained by simple differences in nomenclature.

However, histological diagnoses based on biopsy specimens using the Vienna classification system may result in the underestimation of the neoplastic grade or depth of invasion [8, 9], and this underestimation has been proven in follow-up studies from Western countries [10–15]. HGD frequently progresses to invasive carcinoma over a short period of time, and incidences of progression are 67–85% over mean intervals of 4 months to 1.5 years [10–15]. It is reasonable that such lesions of HGD could initially have been carcinomas but did not transform into carcinomas. In contrast, only 10% of HGD cases were finally diagnosed as carcinoma in a Japanese follow-up study [16]. At the very least, the term well-differentiated adenocarcinoma should be used for HGD.

On the other hand, the most critical point is that even LGD (Vienna Category 3), as defined by Western pathologists, can be diagnosed as well-differentiated adenocarcinoma of low-grade atypia (WD-AC-LG) (Group 5) by Japanese pathologists (Table 5.1). Incidences of progression from LGD to invasive carcinoma were 0–23%

Table 5.1 Comparison between the Vienna classification and Japanese group classification

			Category		
			3	4	5
Group	3	Adenoma	LG-adenoma/LGD		
	4	Suspicious carcinoma		HG-adenoma/HGD	
	5	Carcinoma	Some of LGD	Most of HGD	
				Noninvasive carcinoma	
				Suspicious invasive carcinoma	Invasive carcinoma

in Western studies [10–15] but only 3% in a Japanese study [16]. These results suggest a difference in diagnostic criteria for LGD (including LG adenoma), and in fact, histological features of LGD that have been demonstrated in some reports [17, 18] should be classified as WD-AC-LG by Japanese diagnostic criteria. In order to solve this discrepancy between biopsy and resected specimens, the differential diagnosis between adenoma and WD-AC-LG is critical.

5.2 Differential Diagnosis Between Adenoma and WD-AC-LG

Japanese pathologists have learned and gained experience from routinely assessing large numbers of biopsy specimens provided by endoscopists and from the subsequent feedback gained by examining resected specimens from the same neoplastic lesions. The Japanese diagnostic criteria for intramucosal carcinoma have been established by comparing the histological features of the mucosal component with that of the submucosal component in the same lesion. The intramucosal component of invasive carcinoma should be termed carcinoma if it shows the same cytological features as the submucosal component, regardless of stromal invasion. The invasive ability of carcinoma has already been acquired at a mucosal stage, and therefore, it is logical to make a carcinoma diagnosis based on the cytological features of the mucosal component.

We have also learned that even WD-AC-LG has invasion abilities [19] and the cytological features of WD-AC-LG are different from those of adenoma. The common histological feature of low-grade adenoma and WD-AC-LG is noninvasive, well-differentiated neoplasia with nuclei located at the basal site and low nucleus-to-cytoplasm (N/C) ratio (less than 50%); however, the difference between them is nuclear morphology (shape and arrangement). Adenomas, except for the pyloric gland type, have spindle-shaped nuclei that are regularly arranged at the basal side (Fig. 5.1a), whereas WD-AC-LG has round-to-oval nuclei arranged at the basal area with or without irregular arrangement (Figs. 5.2a and 5.3a).

In addition to our experience, the reasonableness of the Japanese diagnostic criteria has been supported by the following studies. First, the presence of gastric differentiation suggests adenocarcinoma, rather than adenoma, and a follow-up study of borderline lesions revealed that the presence of gastric differentiation is one of the risk factors for malignant transformation [20, 21]. Second, by using the Japanese criteria, the tendency for cell differentiation is different from typical adenoma and has small intestinal differentiation that is distinguished by presence of goblet cells, brush border, and Paneth cells, and the carcinoma tends to express gastric or gastrointestinal differentiation [22, 23]. Third, the incidence and pattern of adipophilin expression are different between adenoma and carcinoma [24]. Fourth, most adenomas tend to have a band-like proliferating zone near the surface, whereas carcinomas tend to have irregularly or diffusely distributed proliferating cells [22–24]. Fifth, genetic abnormalities that are the same as those observed for advanced gastric

carcinoma were detected even in WD-AC-LG [25]. These findings demonstrate that cytological differentiation and distribution of proliferating cells are important for differential diagnoses, in addition to nuclear findings.

The algorithm for differential diagnosis between adenoma and WD-AC-LG is proposed according to nuclear features and cytological differentiation (Fig. 5.4). This is just an algorithm, and for individual cases, intermediate lesions do exist. When the differential diagnosis is difficult, immunohistochemical stains are useful for evaluating cell differentiation through identifying MUC5AC (foveolar cells), MUC2 (goblet cells), MUC6 (pyloric gland and mucous neck cells), and CD10 (small intestinal brush border). Typical adenomas present small intestinal differentiation that is characterized by the presence of goblet cells, brush border, and Paneth

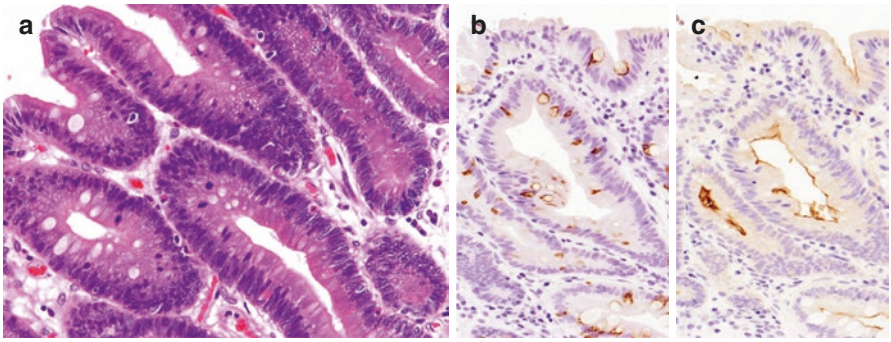

Fig. 5.1 Tubular adenoma. The tumor is composed of columnar epithelium with eosinophilic cytoplasm, admixed with some goblet cells and Paneth cells. The nuclei are spindle-shaped and regularly arranged at the basal side (**a**). Immunohistochemical stains highlight the existence of goblet cells by MUC6 (**b**) and brush border by CD10 (**c**), which indicates small intestinal differentiation

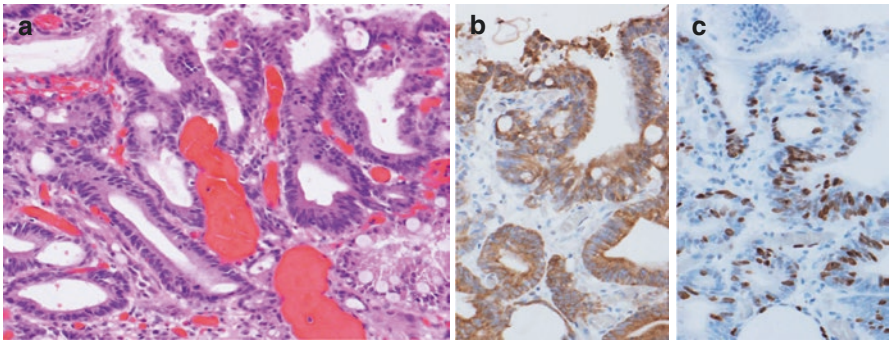

Fig. 5.2 Well-differentiated adenocarcinoma of low-grade atypia. The tumor is composed of columnar epithelium with pale eosinophilic cytoplasm. Neither goblet cell nor Paneth cell is identified. The nuclei are rounded and located at the basal side with an irregular arrangement (**a**). The immunohistochemical stain with MUC5AC reveals gastric foveolar differentiation (**b**). The diffuse distribution f Ki-67 is also characteristic of adenocarcinoma (**c**)

cells (Fig. 5.1b,c), whereas adenocarcinomas tend to express gastric, gastrointestinal, or null phenotypes (Figs. 5.2b and 5.3b). In addition, the evaluation of proliferating cell distributions by Ki-67 is also useful. When Ki-67 positive cells are irregularly or diffusely distributed in the tumor (Figs. 5.2c and 5.3c), it is more likely that the tumor is adenocarcinoma, rather than adenoma [22, 23].

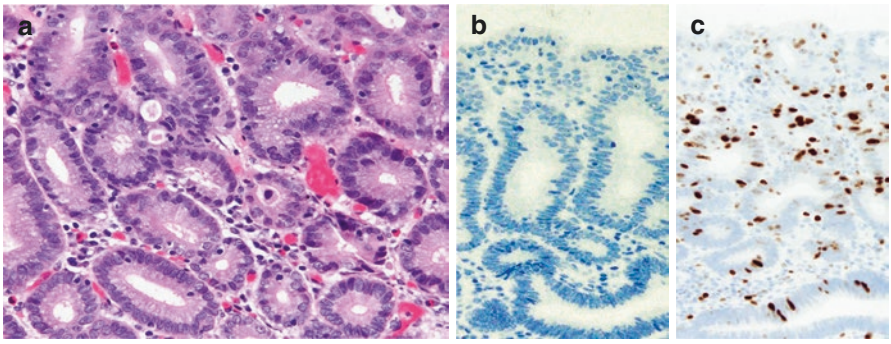

Fig. 5.3 Well-differentiated adenocarcinoma of low-grade atypia. The tumor is composed of columnar epithelium with pale eosinophilic cytoplasm. Neither goblet cell nor Paneth cell is identified. The nuclei are rounded and located at the basal side without an irregular arrangement (**a**). Immunohistochemically, MUC2 (**b**), MUC5AC, MUC6, and CD10 are negative in this tumor, indicating null phenotype. The irregular distribution f Ki-67 is also characteristic of adenocarcinoma (**c**)

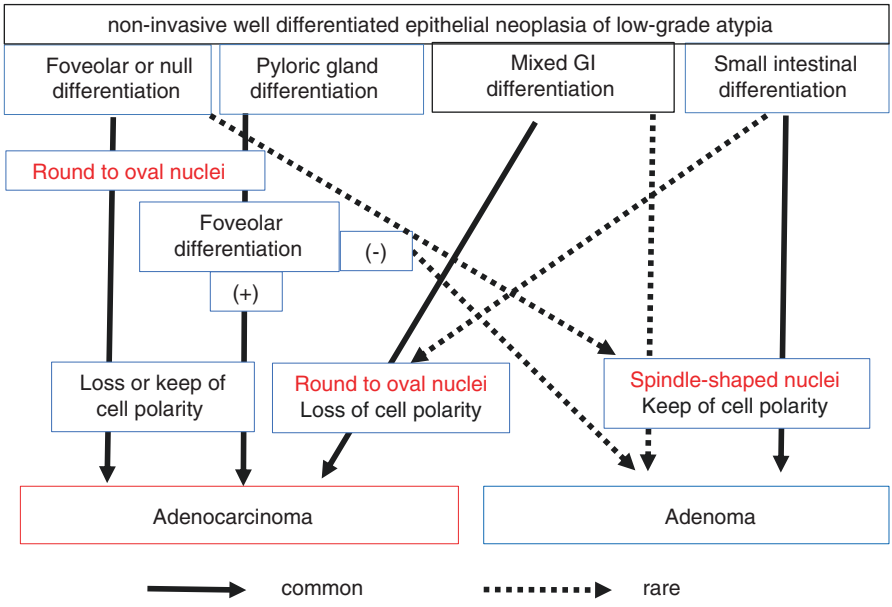

Fig. 5.4 Algorithm of differential diagnosis between adenoma and well-differentiated adenocarcinoma of low-grade atypia

Pyloric gland-type adenomas are a rare and unique variant. Such tumors are mainly composed of mucous cells that are similar to M pyloric gland-type cells (MUC6 positive) and covered by foveolar-type cells (MUC5AC positive). The typical pyloric gland-type adenoma has a proliferating zone near the surface, between foveolar-type cells and pyloric gland-type cells. The irregular or diffuse distribution of proliferating cells and/or diffuse positivity for MUC5AC are characteristics of adenocarcinomas, rather than adenomas.

5.3 Special Types of Gastric Carcinoma in Japanese Classification

The present Japanese histological classification of gastric carcinoma [7] is similar to the WHO classification [26], although there are slight differences. The comparison between Japanese and WHO classifications is shown in Table 5.2. Three histological types of poorly differentiated adenocarcinomas, solid type (por1),

Table 5.2 Comparison between Japanese and WHO classifications

Japanese classification 2017 (15th Ed.)	WHO classification 2010
Common type	
Papillary adenocarcinoma (pap)	Papillary carcinoma
Tubular adenocarcinoma	Tubular carcinoma
Well-differentiated (tub1)	
Moderately differentiated (tub2)	
Poorly differentiated	Poorly cohesive carcinoma
Solid type (por1)	(No description)
Nonsolid type (por2)	
Signet-ring cell carcinoma (sig)	(Included in poorly cohesive carcinoma)
Mucinous carcinoma (muc)	Mucinous carcinoma
(No description)	Mixed adenocarcinoma
Special type	Neuroendocrine neoplasms
Carcinoid tumor	Neuroendocrine tumor (NET), G1 & G2
Endocrine carcinoma	Neuroendocrine carcinoma
(No description)	Mixed adenoneuroendocrine carcinoma
Adenosquamous carcinoma	Adenosquamous carcinoma
Squamous cell carcinoma	Squamous cell carcinoma
Adenocarcinoma with enteroblastic differentiation	(similar to embryonal carcinoma)
Hepatoid adenocarcinoma	Hepatoid adenocarcinoma
Adenocarcinoma of fundic gland type	(No description)
Carcinoma with lymphoid stroma	Carcinoma with lymphoid stroma
Undifferentiated carcinoma	Undifferentiated carcinoma

adenocarcinoma with enteroblastic differentiation (AC-Ent), and adenocarcinoma of fundic gland type (AC-FG), are listed in the Japanese classification but not described in the WHO classification. The clinicopathological characteristics are as follows:

5.3.1 *Poorly Differentiated Solid-Type Adenocarcinoma (por1)*

Adenocarcinoma without glandular formation is classified into poorly differentiated adenocarcinoma, which is further classified into two subtypes: solid type (por1) and nonsolid type (por2). Por1 tends to metastasize through lymphatic channels and disseminate throughout the peritoneum, whereas por1 tend to metastasize through veins. Por1 is frequently accompanied by differentiated components at the tumor periphery [27, 28]. Although por1 can be classified into poorly differentiated-type one, por1 is histogenetically and biologically similar to well-differentiated-type one. Por1 was firstly described in the Japanese classification of gastric carcinoma (12th Ed, 1993), and carcinoma with lymphoid stroma that had previously been categorized as por1 was redefined as special type in the Japanese classification of gastric carcinoma (14th Ed, 2010), because carcinoma with lymphoid stroma is a special type that is associated with EB viral infection. Carcinoma with solid growths, such as hepatoid adenocarcinoma and endocrine carcinoma, should be differentiated by immunohistochemistry.

5.3.2 *Adenocarcinoma with Enteroblastic Differentiation (AC-Ent)*

AC-Ent was first reported by Matsunou [29], and only a few cases have been reported under a different name of clear-cell (glycogen-rich) adenocarcinoma [30, 31]. AC-Ent diagnostic criteria have not been established, and its clinicopathological features have not been clarified, although AC-Ent was introduced in the Japanese classification of gastric carcinoma (14th Ed, 2010) as a miscellaneous carcinoma with a short description.

In 2016, Murakami et al. established the significance of AC-Ent, which has an aggressive biological behavior with high incidence of liver metastasis, and defined AC-Ent as an adenocarcinoma with a clear cytoplasm that resembles fetal gut tissue and displays tubular, papillary, and solid growths with expression of at least one enteroblastic marker (AFP, glypican 3, or SALL4) [32] (Fig. 5.5). Even early-stage AC-Ent has an aggressive biological behavior, which is demonstrated by the high incidence of venous invasion and liver metastasis [32, 33]. Hepatoid adenocarcinoma shares characteristic features with AC-Ent, such as histological features,

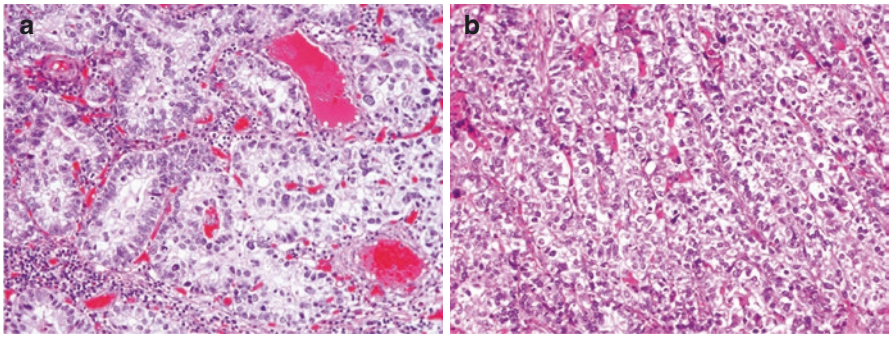

Fig. 5.5 Adenocarcinoma with enteroblastic differentiation. The tumor is composed of clear cytoplasm growing in a tubular structure (**a**) or a solid sheet (**b**)

expression of enteroblastic markers, and high incidence of liver metastasis [34–36]. Therefore, hepatoid adenocarcinoma could be included in the AC-Ent category, as an AC-Ent solid variant.

5.3.3 Adenocarcinoma of Fundic Gland Type (AC-FG)

Adenocarcinoma with chief cell differentiation was first reported by Tsukamoto et al. in 2006 [37], and AC-FG was introduced by Ueyama et al. in 2010 as a new type of gastric adenocarcinoma with distinct clinicopathological characteristics, including tumor location (upper stomach), histological features, phenotypic expression, and low-grade malignancy (low proliferating activity, no lympho-vascular invasion, and good prognosis) [38]. Histologically, AC-FG is defined by epithelial neoplasia that is mainly composed of neoplastic glandular cells that mimic chief and/or parietal cells (Fig. 5.6) and are positive for pepsinogen I and/or H^+/K^+-ATPase. Almost all cases of AC-FG were positive for pepsinogen I and MUC6, which suggests that AC-FG is mainly composed of carcinoma cells with immature differentiation toward chief cells [39]. AC-FG usually shows very low N/C ratio and resembles fundic glands, and therefore, diagnosis using a biopsy specimen is sometimes difficult.

AC-FG, especially when restricted to the mucosa, is recommended by Western pathologists to be classified as an oxyntic gland polyp/adenoma [40]. Although AC-FG is a low-grade malignancy, this mucosal lesion without metastatic potential should be treated as a carcinoma and undergo endoscopic resection before acquiring metastatic potential. Recently, aggressive variants with lympho-vascular invasion or intramural metastasis have been found [41, 42], and more recently, AC-FG was identified to lack association with *Helicobacter pylori* infection [41, 43]. More attention should be paid to AC-FG now and in the future.

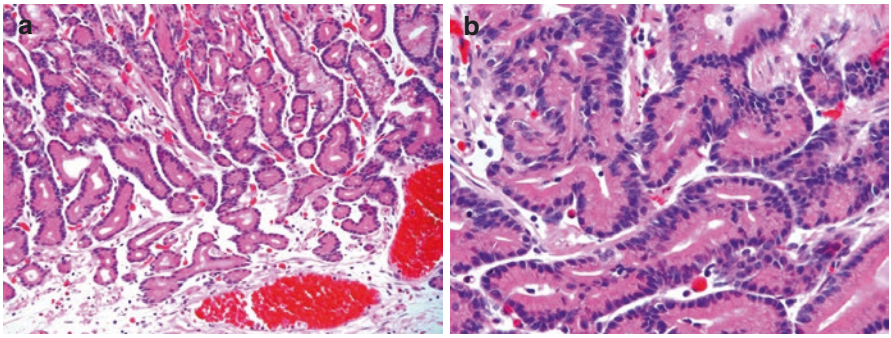

Fig. 5.6 Adenocarcinoma of fundic gland type. The tumor is composed of highly differentiated columnar cells mimicking fundic gland cells, predominantly chief cells, with pale gray-blue, basophilic cytoplasm and mildly enlarged nuclei, growing in an irregular tubular structure (**a**, **b**)

5.4 Histological Evaluation of Endoscopically Resected Specimens

Curative endoscopic resections should be performed for carcinomas with low risk of lymph node metastasis, and the incidence of lymph node metastasis for intramucosal gastric carcinoma has been reported to be approximately 2% [44–47].

The Japanese gastric cancer treatment guidelines (2014, ver.4) have provided indication of curative endoscopic resections [48] (Fig. 5.7). The curability of endoscopic resection is evaluated by histological examination of the status of resected margin, tumor size, histological type, depth of invasion, presence of ulcer (including scar), and lympho-vascular invasion.

In order to evaluate the histological details, the proper treatment of the resected specimen is essential. It should be extended with pins on the board, fixed in 10% formalin solution, and completely cut in stepwise sections 2–3 mm in width. A record of macroscopic pictures before and after sectioning is also recommended [49].

With regard to histological type, the predominant histological type is usually representative of the lesion. Even if the representative type is a differentiated type, the presence of a poorly differentiated component increases the risk of metastasis [44, 47]. As our knowledge of differentiated-type adenocarcinomas that are accompanied with some areas of undifferentiated components is currently insufficient, such tumors are regarded as non-curative for the time being, and additional surgical treatments are recommended.

The significance of papillary adenocarcinoma (pap) has not been described in the Japanese guideline. Although pap is classified as a differentiated-type adenocarcinoma, pap is known to be an adverse prognostic factor by a higher risk of lympho-vascular invasion and metastasis to the lymph nodes and liver, compared with tubular adenocarcinoma [50–52]. This tendency was confirmed by analysis on endoscopically resected gastric cancers [53].

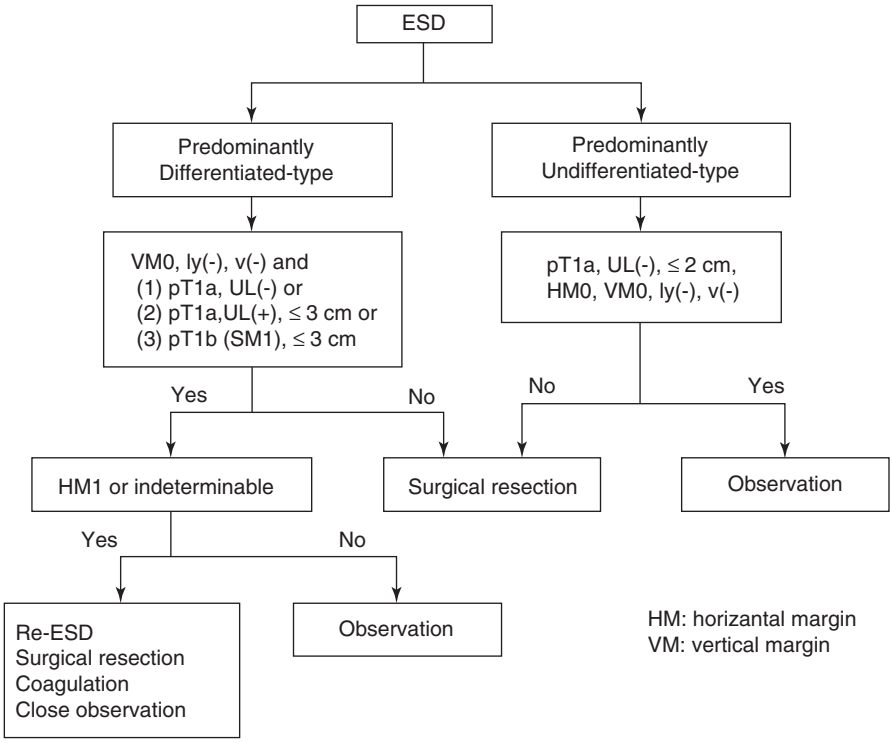

Fig. 5.7 Treatment options after endoscopic resection from Japanese gastric cancer treatment guideline 2014 [4]

References

1. Schlemper RJ, Itabashi M, Kato Y, et al. Differences in diagnostic criteria for gastric carcinoma between Japanese and Western pathologists. Lancet. 1997;349:1725–9.
2. Schlemper RJ, Itabashi M, Kato Y, et al. Differences in the diagnostic criteria used by Japanese and Western pathologists to diagnose colorectal carcinoma. Cancer. 1998;82:60–9.
3. Schlemper RJ, Riddell RH, Kato Y, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut. 2000;47:251–5.
4. Schlemper RJ, Kato Y, Stolte M. Review of histological classifications of gastrointestinal epithelial neoplasia: differences in diagnosis of early carcinomas between Japanese and Western pathologists. J Gastroenterol. 2001;36:445–56.
5. Lauwers GY, Shimizu M, Correa P, et al. Evaluation of gastric biopsies for Neoplasia: differences between Japanese and Western Pathologists. Am J Surg Pathol. 1999;23:511–8.
6. Riddell RH, Iwafuchi M. Problems arising from eastern and western classification systems for gastrointestinal dysplasia and carcinoma: are they resolvable? Histopathology. 1998;33:197–202.
7. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma. 15th ed. Tokyo: Kanehara; 2017.
8. Cho SJ, Choi IJ, Kim CG, et al. Risk of high-grade dysplasia or carcinoma in gastric biopsy-proven low-grade dysplasia: an analysis using the Vienna classification. Endoscopy. 2011;43:465–71.

9. Yoshida M, Shimoda T, Kusafuka K, et al. Comparative study of Western and Japanese criteria for biopsy-based diagnosis of gastric epithelial neoplasia. Gastric Cancer. 2015;18:239–45.
10. Saraga EP, Gardiol D, Costa J. Gastric dysplasia. A histological follow-up study. Am J Surg Pathol. 1987;11:788–96.
11. Rugge M, Farinati F, Di Mario F, et al. Gastric epithelial dysplasia: a prospective multicenter follow-up study from the interdisciplinary group on gastric epithelial dysplasia. Hum Pathol. 1991;22:1002–8.
12. Farinati F, Rugge M, Di Mario F, et al. Early and advanced gastric cancer in the follow-up of moderate and severe gastric dysplasia patients. A prospective study. I.G.G.E.D.-interdisciplinary group on gastric epithelial dysplasia. Endoscopy. 1993;25:261–8.
13. Di Gregorio C, Morandi P, Fante R, et al. Gastric dysplasia. A follow-up study. Am J Gastroenterol. 1993;88:1714–9.
14. Rugge M, Farinati F, Baffa R, et al. Gastric epithelial dysplasia in the natural history of gastric cancer: a multicenter prospective follow-up study. Gastroenterology. 1994;107:1288–96.
15. Kokkola A, Haapiainen R, Laxen F, et al. Risk of gastric carcinoma in patients with mucosal dysplasia associated with atrophic gastritis: a follow up study. J Clin Pathol. 1996;49:979–84.
16. Yamada H, Ikegami M, Shimoda T, et al. Long-term follow-up study of gastric adenoma/ dysplasia. Endoscopy. 2004;36:390–6.
17. Sung JK. Diagnosis and management of gastric dysplasia. Korean J Intern Med. 2016;31:201–9.
18. Lee CK, Chung IK, Lee SH, Kim SP, Lee SH, Lee TH, et al. Is endoscopic forceps biopsy enough for a definitive diagnosis of gastric epithelial neoplasia? J Gastroenterol Hepatol. 2010;25:1507–13.
19. Yao T, Utsunomiya T, Oya M, Nishiyama K, Tsuneyoshi M. Extremely well-differentiated adenocarcinoma of the stomach: clinicopathological and immunohistochemical features. World J Gastroenterol. 2006;12:2510–6.
20. Kolodziejczyk P, Yao T, Oya M, et al. Long term follow-up study of patients with gastric adenomas with malignant transformation. Cancer. 1994;74:2896–907.
21. Fuchigami T, Iwashita A, Sakai Y, et al. Gastric benign/borderline lesion diagnosed as Group III by biopsy specimen: diagnostic problems from the viewpoint of long-term clinical course. Stomach Int. 1994;29:153–67. (in Japanese with English abstract).
22. Minematsu H, Satito Y, Kakinoki R, et al. Evaluation of mucin expression patterns in gastric borderline (group III) lesions. J Gastroenterol. 2006;41:547–53.
23. Gushima R, Yao T. Pathological differentiation of adenomas and differentiated-type adenocarcinoma of the stomach—gastric adenoma with an intestinal phenotype. Stomach Int. 2014;49:1827–36. (in Japanese with English abstract).
24. Gushima R, Yao T, Kurisaki-Arakawa A, et al. Expression of adipophilin in gastric epithelial neoplasia is associated with intestinal differentiation and discriminates between adenoma and adenocarcinoma. Virchow Arch. 2016;468:169–77.
25. Kukshima R, Mukaisho K, Tsukashita S, et al. Molecular biological characteristics of early stomach adenocarcinomas of the completely gastric phenotype revealed by laser capture microdissection and comparative genomic hybridization. Stomach Int. 2003;38:707–21. (in Japanese with English abstract).
26. Lauwers GY, Carneiro F, Graham DY, et al. Tumors of the stomach. In: Bosman FT, Carneiro F, Hurban RH, Theise ND, editors. WHO classification of tumours of the digestive system. Lyon, France: IARC Press; 2010. p. 45–58.
27. Ueyama T, Tsuneyoshi M. Poorly differentiated solid type adenocarcinomas in the stomach: a clinicopathologic study of 71 cases. J Surg Oncol. 1992;51:81–7.
28. Adachi Y, Mori M, Maehara Y, et al. Poorly differentiated medullary carcinoma of the stomach. Cancer. 1992;70:1462–6.
29. Matsunou H, Konishi F, et al. Alpha-fetoprotein-producing gastric carcinoma with enteroblastic differentiation. Cancer. 1994;73:534–40.
30. Govender D, Ramdial PK, Clarke B, et al. Clear cell (glycogen-rich) gastric adenocarcinoma. Ann Diagn Pathol. 2004;8:69–73.

31. Ghotli ZA, Serra S, Chetty R. Clear cell (glycogen rich) gastric adenocarcinoma: a distinct tubulo-papillary variant with a predilection for the cardia/gastro-oesophageal region. Pathology. 2007;39:466–9.
32. Murakami T, Yao T, Mitomi H, et al. Clinicopathologic and immunohistochemical characteristics of gastric adenocarcinoma with enteroblastic differentiation: a study of 29 cases. Gastric Cancer. 2016;19:498–507.
33. Matsumoto K, Ueyama H, Matsumoto K, et al. Clinicopathological features of alpha-fetoprotein producing early gastric cancer with enteroblastic differentiation. World J Gastroenterol. 2016;22:8203–10.
34. Ushiku T, Shinozaki A, Shibahara J, et al. SALL4 represents fetal gut differentiation of gastric cancer, and is diagnostically useful in distinguishing hepatoid gastric carcinoma from hepatocellular carcinoma. Am J Surg Pathol. 2010;34:533–40.
35. Ushiku T, Uozaki H, Shinozaki A, et al. Glypican 3-expressing gastric carcinoma: distinct subgroup unifying hepatoid, clear-cell, and alpha-fetoprotein-producing gastric carcinomas. Cancer Sci. 2009;100:626–32.
36. Kinjo T, Taniguchi H, Kushima R, et al. Histologic and Immunohistochemical analyses of a-fetoprotein producing Cancer of the stomach. Am J Surg Pathol. 2012;36:56–65.
37. Tsukamoto T, Yokoi T, Maruta S, et al. Gastric adenocarcinoma with chief cell differentiation. Pathol Int. 2007;57:517–22.
38. Ueyama H, Yao T, Nakashima Y, et al. Gastric adenocarcinoma of fundic gland type (chief cell predominant type): proposal for a new entity of gastric adenocarcinoma. Am J Surg Pathol. 2010;34:609–19.
39. Ota H, Yamaguchi D, Iwaya M, et al. Principal cells in gastric neoplasia of fundic gland (chief cell predominant) type show characteristics of immature chief cells. Pathol Int. 2015;65:202–4.
40. Singhi AD, Lazenby AJ, Montgomery EA. Gastric adenocarcinoma with chief cell differentiation: a proposal for reclassification as oxyntic gland polyp/adenoma. Am J Surg Pathol. 2012;36:1030–5.
41. Yao T, Ueyama H, Kushima R, et al. New type of gastric carcinoma-adenocarcinoma of the Fundic gland type: its clinicopathological features and tumor development. Stomach Int. 2010;45:1192–202.
42. Ueo T, Yonemasu H, Ishida T. Gastric adenocarcinoma of fundic gland type with unusual behavior. Dig Endosc. 2014;26:293–4.
43. Ueyama H, Matsumoto K, Nagahara A, et al. Gastric adenocarcinoma of the fundic gland type (chief cell predominant type). Endoscopy. 2014;46:153–7.
44. Oya M, Yao T, Nagai E, et al. Metastasizing intramucosal gastric carcinomas. Well differentiated type and proliferative activity using proliferative cell nuclear antigen and Ki-67. Cancer. 1995;75:926–35.
45. Gotoda T, Yanagisawa A, Sasako M, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer. 2000;3:219–25.
46. Song SY, Park S, Kim S, et al. Characteristics of intramucosal gastric carcinoma with lymph node metastatic disease. Histopathology. 2004;44:437–44.
47. Tanabe H, Iwashita A, Haraoka S, et al. Clinicopathological characteristics of intramucosal gastric carcinoma with lymph node metastasis. Stomach Int. 2006;41:1119–29. (in Japanese with English abstract).
48. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer. 2017;20:1–219.
49. Ono H, Yao K, Fujishiro M, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. Dig Endosc. 2016;28:3–115.
50. Yasuda K, Adachi Y, Shiraishi N, et al. Papillary adenocarcinoma of the stomach. Gastric Cancer. 2000;3:33–8.
51. Nakashima Y, Yao T, Hirahashi M, Aishima S, Kakeji Y, Maehara Y, Tsuneyoshi M. Nuclear atypia grading score is a useful prognostic factor in papillary gastric adenocarcinoma. Histopathohlogy. 2011;59:841–9.

52. Sekiguchi M, Kushima R, Oda I, et al. Clinical significance of a papillary adenocarcinoma component in early gastric cancer: a single-center retrospective analysis of 628 surgically resected early gastric cancers. J Gastroentrol. 2015;50:424–34.
53. Sekiguchi M, Sekine S, Oda I, et al. Risk factors for lymphatic and venous involvement in endoscopically resected gastric cancer. J Gastroenterol. 2013;48:706–12.