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Editorial

Low-Grade, Well-Differentiated Gastric Tubular Adenocarcinoma (LG-Tub1): Why should it be noticed now ?

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1. Keywords: Low-grade, well-differentiated tubular adenocarcinoma; Narrow-band imaging; Magnifying endoscopy; Differential diagnosis; Endoscopic submucosal dissection; Histologically mixed type; Premalignant gastric neoplasia; Gastric mucin phenotype; Gastric cancer after successful *Helicobacter pylori* eradication therapy; Gastric cancer without *Helicobacter pylori* infection; Early gastric cancer.

2. Editorial

General type gastric cancer (GC) lesions are classified according to differentiation degree; into Papillary Adenocarcinoma (pap), Tubular Adenocarcinoma (tub), Poorly Differentiated Adenocarcinoma (por), Signet-Ring Cell Carcinoma (sig), and Mucinous Adenocarcinoma (muc). Additionally, tub lesions are subdivided into well- and moderately differentiated tub (tub1 and tub2, respectively). Por lesions are subdivided into solid (por1) and non-solid (por2) types [1]. The differentiation degree indicates how similar the structure of cancerous parts is to that of non-cancerous parts. Malignant biological characteristics become greater in contra proportion to differentiation degree (synonymous with structural atypia grade). Thus, the lower the structural atypia grade is, the greater malignant biological characteristics become.

Additionally, general type GC lesions are also classified into differentiated- (pap, tub1, and tub2) and undifferentiated- (por1, por2, sig, and muc) types [2] (synonymous with intestinal and diffuse types, respectively [3]).These classifications reflect the endoscopic features and malignant biological grades; of each of the types.

Moreover, general-type GC lesions are classified according to cytological and glandular architectural atypia; into Low-Grade (LG) and High-Grade (HG) [4]. The atypia grade indicates how different the glandular architecture and cytological atypia of cancerous parts are from those of noncancerous part. Malignant biological characteristics become greater in proportion to atypia grade, synonymous with cytological and glandular architectural atypia grade. Thus, the higher the atypia grade is, the higher the malignant biological characteristics become.

Therefore, all combinations between atypia grade and differentiation degree can exist. However, among the types of GC, which consists of a single (synonymous with pure) histological type, LG undifferentiated-type GC is extremely rare, LG-tub2 is less frequent, and LG-pap is rare and most of the undifferentiated-type GCs exhibit not LG but HG [5-8]. Accordingly,

the undifferentiated-type GC, if not described accompanied by HG or LG, is considered to mean HG [5-8].

In fact, there are many histologically mixed-type GC lesions that consist of the combinations of differentiated- or undifferentiated-types and LG or HG; e.g. LG-tub1 containing HG-tub2 and (HG-) por2, and HG-tub2 containing (HG-) por2 and (HG-) sig, etc. It is well known that histologically mixed-type GC exhibits more malignant characteristics than pure GC. It was also reported that; among GC of the pure differentiated-type, pure undifferentiated-type, mixed of differentiated-type and undifferentiated-type, HG undifferentiated-type-predominant mixed-type GC exhibits the highest frequency of lymph node metastasis [9].

Apart from these classifications, one Japanese pathologist proposed the Japanese term 'low-grade, differentiated-type gastric cancer'10 years before [10].This term meant one category consisting of LG-tub1, LG-tub2, and LG-pap. Another Japanese pathologist made a report in Japanese using this term [11].Because these English terms mentioned by the two pathologists are subtly different from the accurate English translation of Japanese "low-grade, differentiated-type gastric cancer; , these terms, especially the English term "low-grade, well-differentiated adenocarcinoma of the stomach", are considered easily confused with LG-tub1 (low-grade, well-differentiated tubular adenocarcinoma) of the stomach, so careful attention is needed to not confuse these terms when they are used.

Attention has been being focused on gastric cancer without *Helicobacterpylori (H. pylori)* Infection [12]. GC of fundic gland type and gastric foveolar-type adenocarcinoma, which are proposed as new entities of GC, are included in GC without *H. pylori* infection [13, 14]. GC of fundic gland type is classified into special type and not general type [1]. Although GC of fundic gland type has a higher frequency of SM invasion (50~52%), lymph node metastasis derived from this is rare [14, 15]. Additionally, although the authors of the first report of this cancer described that this cancer was "well-differentiated adenocarcinoma", it is supposed to have meant that this cancer differentiated well toward chief cells [13]. Caution must be taken so that this cancer is not confused as "low-grade, differentiated-type GC" [10, 11] of the general type [1]. The gastric foveolar-type adenocarcinoma not classified yet by Japanese classification of gastric carcinoma and is classified as adenoma in Western [16]. Gastric foveolar-type adenocarcinoma is intraepithelial cancer and exhibits no metastasis. These two types of GCs without *H. pylori* infection are less malignant. Additionally, GC without *H. pylori* infection is rare (approximately 0.66~3% of GC) [12].

Additionally, in our clinical field, most low-grade, differentiated-type gastric cancer lesions are LG-tub1 [5-8]. Moreover, in Japan, the histological type and subtype of gastric cancer are stipulated to be recorded according to Japanese classification of gastric carcinoma. In the case of histologically mixed-type gastric cancer lesions that consist of more than one histological subtype, the different histological components are stipulated to be recorded in descending order of the occupied surface area [1]. From the above, it can be considered rather suitable to record the histological type and subtype of the low-grade gastric cancer lesions of differentiated-type as LG-tub1, LG-tub2, and LG-pap [8], not as the English terms mentioned by the two pathologists [10, 11]. For example, although mixed-type LG-tub1 (M-LG-tub1) lesions, which consist of predominant LG-tub1 and minor other histological atypia grades and subtypes, occasionally include the HG-tub2 component, it is enough for such lesions to be recorded as LG-tub1>HG-tub2 [8].

From the standpoint of gastrointestinal endoscopists, among LG-tub1, some lesions are difficult to diagnose such as those having less remarkable findings in their surfaces and exhibiting isochromatic color and unclear demarcation line (DL) by white light endoscopy (WLE) [7, 8, 17].LG-tub1, which invades the submucosal (SM) [1] layer and deepens without changing the atypia-grade and/or histological subtype of the invaded part, is rare (approximately 1.2% of GC) [18]. However, an LG-tub1 lesion that was not firmly diagnosed at the time it was noticed as an SM invasive gastric tumor but was firmly diagnosed as remaining LG-tub1 in the whole tumor after surgical therapy was reported [19]. Another LG-tub1 lesion that had invaded deeper than the SM layer whose invaded part had changed to HG-tub2 and undifferentiated-type cancerous components at the time it was noticed was reported [20].Therefore, careful notice should be taken when diagnosing LG-tub1 lesions.

Eradication therapy for *H. pylori* has been ongoing [21]. Consequently, GC after successful *H. pylori* eradication therapy has been attracting attention [21-23]. GC after successful *H. pylori* eradication therapy has four to ten times higher frequency than GC without *H. pylori* infection, and most of this type of cancer is differentiated [23, 24]. Additionally, it was reported that LG-tub1 lesions occupied approximately 38% of this type of cancer [24]. It was also reported that LG-tub1 lesions occupied approximately 34% of early GCs and approximately 57% of the LG-tub1 lesions was after spontaneous eradication and after successful eradication therapy, for *H. pylori* [8]. Therefore, the significance of the diagnosis and treatment of LG-tub1 in early gastric cancer is increasing.

Recently, with the advent of gastrointestinal high-resolution endoscopy and the development and spread of Imaging Enhanced Endoscopy (IEE), such as Narrow-Band Imaging (NBI) with magnifying

endoscopy (ME; NBI-ME), LG-tub1 lesions that can be diagnosed before extensive lateral spreading and SM invasion are considered increasing [7, 8]. It was reported that low-risk pure LG-tub1 (P-LG-tub1) and high risk M-LG-tub1 can be distinguished with high diagnostic accuracy (88.9%) by NBI-ME [7], that LG-tub1 containing a minor HG-tub2 component (LG-tub1>HG-tub2) lesions among M-LG-tub1 have a higher frequency of reddish color, superficial depressed (0-IIc) shape, and gastric mucin phenotype [8], and that gastric-mucin-phenotype LG-tub1>HG-tub2 lesions, in proportion to their diameters, can be partly changed from LG to HG and include undifferentiated-type components and thus have the highest malignant characteristics among LG-tub1 lesions [8]. It was also reported that GC after successful *H. pylori* eradication therapy has a higher frequency of reddish color and superficial depressed (0-IIc) shape [25]. This type of cancer is probably considered homologous to LG-tub1>HG-tub2 in shape and color. Moreover, it was reported that among these types of cancer lesions that invaded SM and deeper, approximately 72% were differentiated-type lesions and approximately 22% were mixed-type lesions [26]. Furthermore, it was reported that LG-tub1 may become HG-tub1 and even HG-tub2 in proportion to their diameter [4, 7-8]. In other words, among gastric cancer lesions that invaded the SM layer and deeper after successful *H.pylori*eradication, it might be suggested that SM-and-deeper-invaded differentiated-type GC lesions of this type (e.g. HG-tub1>HG-tub2) can proceed from LG-tub1>HG-tub2 lesions and that SM-and-deeper-invaded mixed-type GC lesions of this type (e.g. HG-tub1>HG-tub2>por2) can proceed from gastric-mucin-phenotype LG-tub1>HG-tub2 lesions containing undifferentiated-type components.

Therefore, in many countries where eradication therapy for *H. pylori* has been proceeding, the diagnosis of LG-tub1 which is frequent among gastric cancer lesions after successful *H.pylori* eradication, especially the diagnosis of M-LG-tub1, including LG-tub1>HG-tub2, which might have higher malignant potential, is important.

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