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Architectural pattern of gastric adenocarcinoma – A 3-dimensional reconstruction study

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Summary. The 3-D microstructure of various adenocarcinomas was studied by graphic reconstruction of tubules and lumina from serial sections in four gastrectomy specimens in order to contribute to better diagnosis of the lesion by establishing the morphology of atypical glands. The cell nests in the moderately differentiated type had multiple anastomoses with one another forming a network, a pattern different from arborescent normal glands, while the lumina were separated into many small vesicles, giving the nests a porous character. Well differentiated tumors had more connections between the lumina forming a luminal network, whereas in the poorly differentiated lesions the nests also began to split into fragments. These findings provided a new viewpoint from which to establish an architectural basis for the discrimination of dysplastic from overtly malignant lesions.

Key words: Gastric carcinoma – Pathology – 3-D microstructure

Pathologists' diagnosis of adenocarcinoma depends not only on the recognition of cellular abnormality but also on identification of strikingly bizarre shapes of glands. The former finding has been and is the subject of a vast amount of studies, while the latter is only poorly formulated into definite criteria. Systematic understanding in this field is still lacking, although its diagnostic importance has been stressed many times. Gland form however, if defined on a strict morphological basis, would be quite helpful in discriminating so-called borderline cases from well differentiated adenocarcinoma. So, in order to establish a basis for this aspect of morphology, we attempted reconstruction studies of gastric adenocarcinomas.

Materials and Methods

Four gastrectomy specimens with adenocarcinoma of various types served as material (one well differentiated, two moderately and one poorly differentiated); these nomenclatures comply with the classification by the Japanese Research Society for Gastric Cancer (1974). Ordinary

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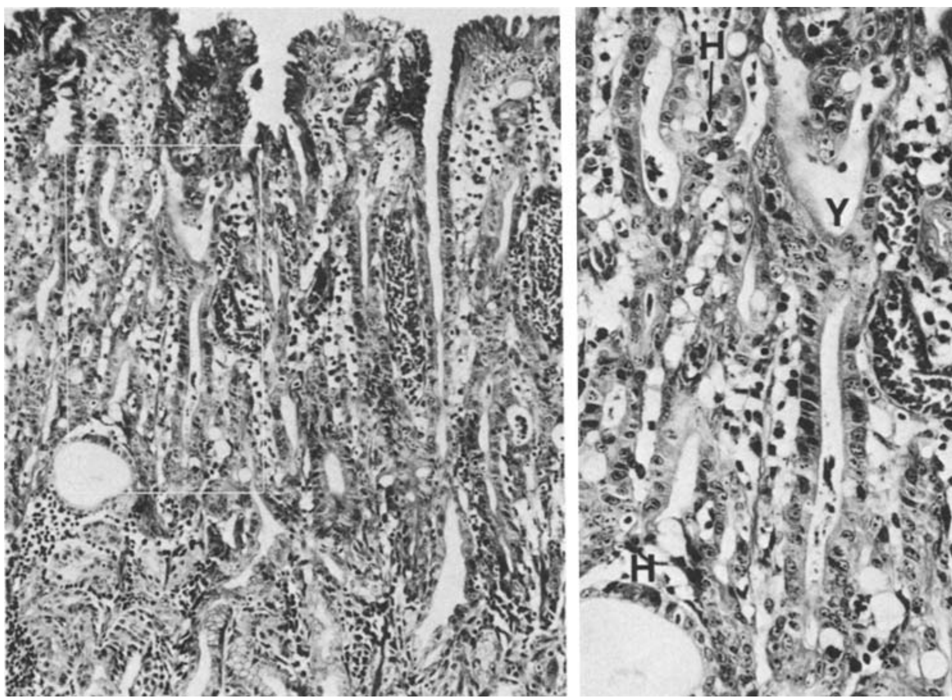


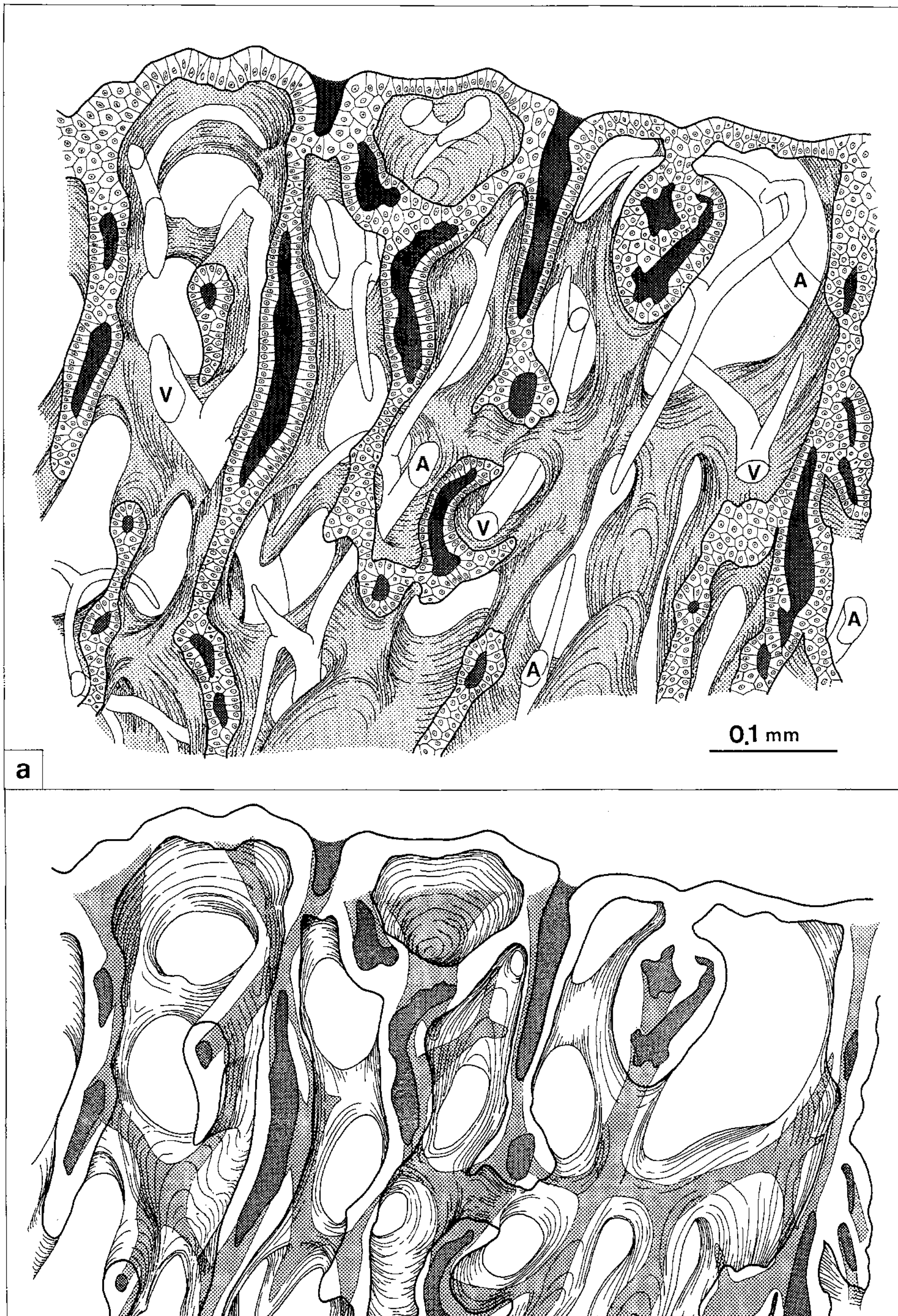
Fig. 1. (*Left*) Well differentiated tubular adenocarcinoma growing in the superficial mucosa of a IIc-lesion. Partially dilated fundic glands are seen at the mucosal bottom. H.E. ×120. (*Right*) Higher magnification of the square area in the left figure. Note the markedly abnormal architecture of glands with anastomoses producing X·Y·H-patterns. *Y*: Y-pattern. *H*: H-pattern. H.E. ×240

gastric glands were studied in an apparently normal stomach from a patient operated on for duodenal ulcer. From each tumor 200 serial sections 3.5 μ thick were prepared and were stained with Azan-Mallory stain. Reconstruction of tumor tissue was performed by a graphic method, details are described elsewhere (Takahashi and Iwama: Atypical glands in gastric adenoma. Three-dimensional architecture compared with carcinomatous and metaplastic glands, submitted to Virchows Arch [Pathol Anat]). The results of 3-D observations were presented in a stereogram. We also attempted to simplify the actual structure of adenocarcinoma into its basic skeleton, and to describe the variously framed skeletons in geometric terms. This was indispensable in analyzing how adenocarcinoma differed, as an example, from gastric adenomas.

Results and Discussion

The ordinary architecture of fundic as well as pyloric glands was simple with a few dichotomies at lower foveola and glandular bottom. There was no anastomosis between adjacent tubules.

Fig. 2. a (*upper*) Reconstruction of carcinomatous tubules from the well differentiated adenocarcinoma of Fig. 1. The upper margin corresponds to the mucosal surface. The tubules form a 3-D network with many loops and closely intertwine with small blood vessels (*A*: artery and *V*: vein). **b** (*lower*) The same portion is reproduced to show the luminal spaces (shaded) which also are united in the form of network



A
V
A
V
V
A
A
0.1 mm
a
b

The *well differentiated adenocarcinoma* we analyzed presented macroscopically as a depressed lesion of mucosa (type IIc) where the glands, while lined with seemingly well differentiated cells, were arranged in an evidently bizarre fashion; a net-like disarray of tubules described by Ohta (1964) as X·Y·H-shape in contrast to the reverse-Y of ordinary glands (Fig. 1). Reconstruction of this mucosal zone in Fig. 2a reveals multiply anastomosing tubules forming a 3-D network with many loops. Apparently this contrasts sharply with the arborescent glands of normal stomach and is responsible for generating bizarre patterns in 2-D sections. It is also shown that the carcinomatous tubules closely intertwine with small arteries and veins; this may be because carcinoma always grows while co-existing with a network of blood vessels, which may account for the formation of the network skeleton. Also, the lumina are shown to be knit into another network (Fig. 2b) although there are places where the lumen is disconnected, suggesting somewhat lower connectivity of lumina than tubules. It should be noted that the lumina in this case are united as a whole, unlike the cases that follow. We regard this unity as the distinctive feature of well differentiated adenocarcinoma.

The *moderately differentiated adenocarcinoma,* the most common gastric tumor, was represented by a submucosally invading portion in one of the two cases analyzed. The microscopical appearance included irregularly interconnected cell nests, back-to-back pattern and marked dysplasia of stratified cells (Fig. 3a). Three-dimensionally, the tubular nests are again connected to form a network with many loops (Fig. 3b), but on the other hand the lumina are no longer continuous and are split into many vesicles without forming any loop whatever. This describes a spongy structure; we prefer to call this a "porous" condition and clearly this porosity corresponds to the back-to-back pattern, a 2-D feature that has been assumed to be specific for adenocarcinoma in general. In addition, the separated lumina have a hole in the epithelial lining apparently due to retention and rupture. In microscopic slides, a ruptured gland appears as flatly transformed or crescentic in section, which works as another marker for adenocarcinoma.

The last type, the *poorly differentiated,* corresponds to the diffuse carcinoma of Lauren (1965). Small nests comprizing only a few cells, sometimes with a small lumen, were scattered in the stroma (Fig. 4a). They appeared to infiltrate individually, and this impression was justified by reconstruction shown in Fig. 4b in which, although the major part of nests still retain a united network, fragmented nests have already begun to separate from it and are moving into the stromal space.

The 3-D microstructure of adenocarcinomas visualized above was classified according to the geometry of skeletons (Fig. 5). This is to apply the topological parameters p_0 and p_1 to both nests and lumina, a method introduced into pathological study by the senior author (Takahashi, 1978). Of these, p_0 is called the 0-th Betti number and describes the number of separate parts in a structure. p_1, the 1st Betti number, is the number of anastomoses a network contains. In well differentiated adenocarcinoma, 1 mm^3 tumor contains 384 anastomoses among lumina, demonstrating a dense luminal

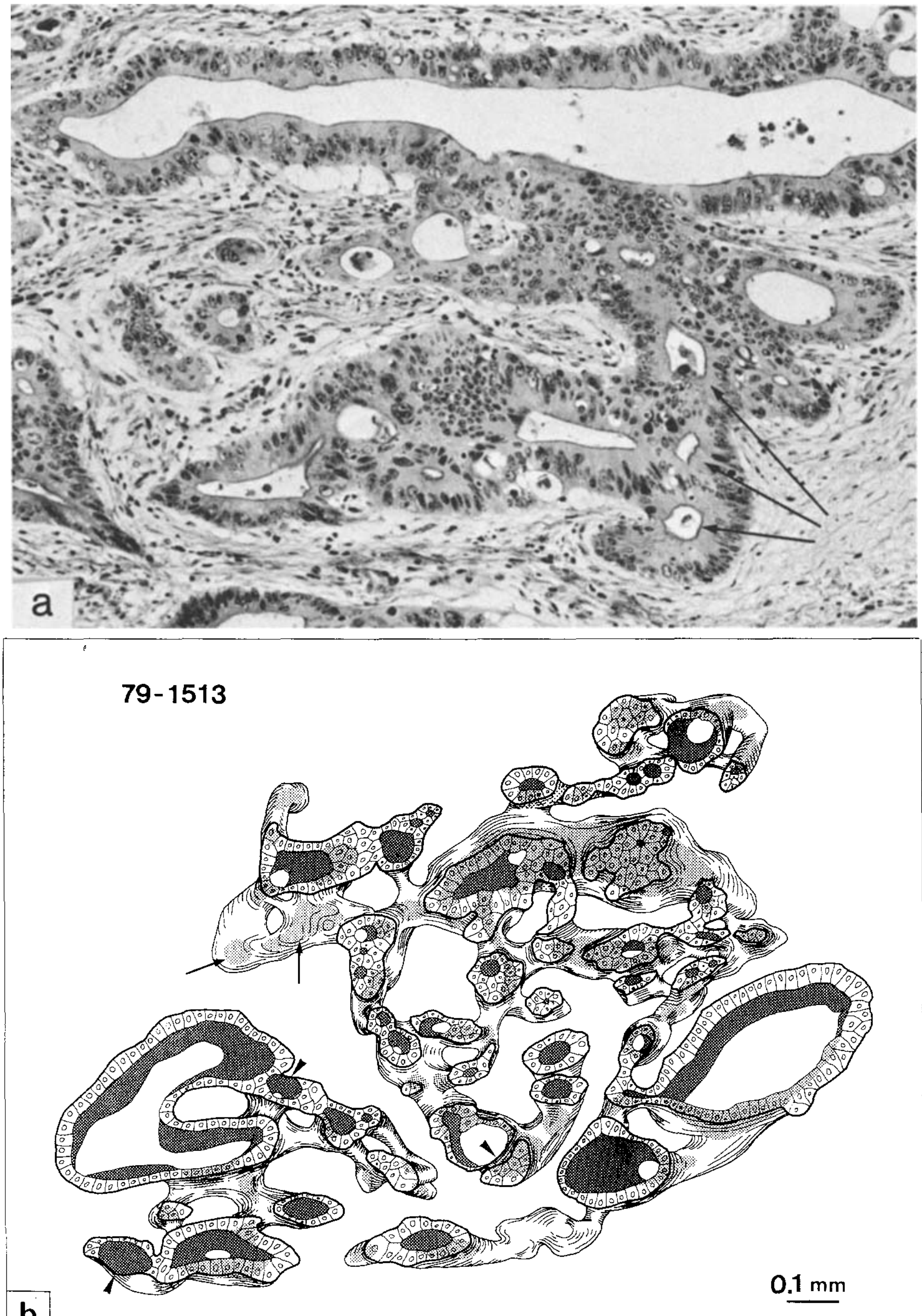


Fig. 3. a (*upper*) Moderately differentiated adenocarcinoma. Apart from dysplastic changes, a bizarre glandular pattern is striking with irregular interconnection of tubules and back-to-back patterns (*arrows*). H.E. ×110. **b** (*lower*) Reconstruction from the above tumor. The cellular nests are multiply connected to form a network. The shaded spots are the vesicular lumina hidden within the nests (*arrows*). The arrowheads point at the rupture site of the overdistended lumina

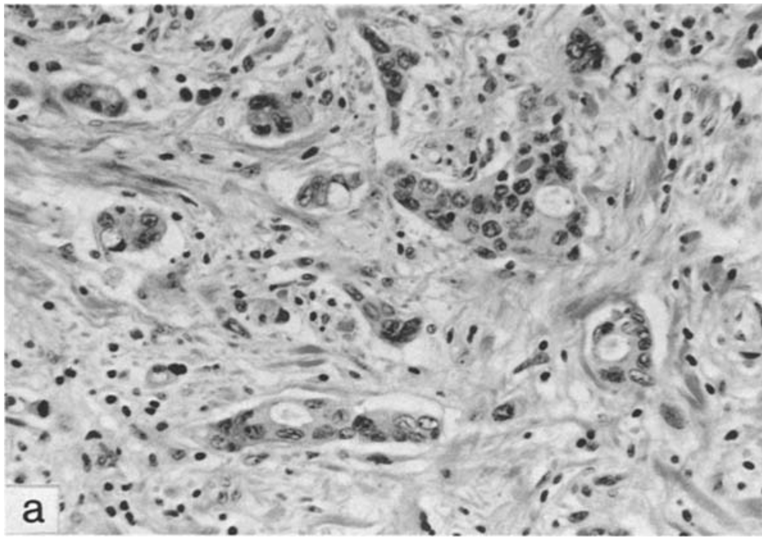


Fig. 4. **a** (*upper*) Poorly differentiated adenocarcinoma with small irregular clusters dispersed in the broad stroma. H.E. ×320. **b** (*lower*) Reconstruction from the above tumor. There remains a network made of porous nests, but the major part has already begun to split into small fragments. The arrows indicate ruptured lumina

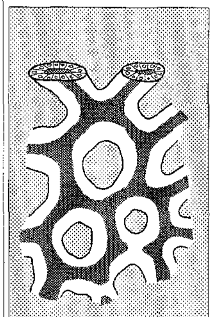
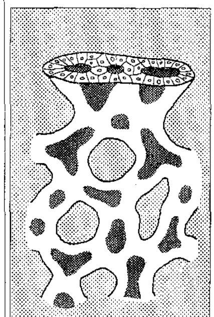
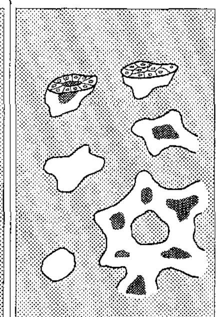
	Well d.a.	Moderately d.a.	Poorly d.a.
topology			
p_0 (number of separate parts /mm^3)			
Nest	1	1	871
Lumen	1	439	1133
p_1 (number of inner connection /mm^3)			
Nest	1640	287	653
Lumen	384	0	0

Fig. 5. Description of architectural patterns with topological variables p_0 and p_1. *Well d.a.*: Well differentiated adenocarcinoma; *Moderately d.a.*: Moderately differentiated adenocarcinoma; *Poorly d.a.*: Poorly differentiated adenocarcinoma; Each set of values expresses the geometric properties of respective type of carcinoma

network ($p_1 = 384$). The number of separate parts (p_0) is 1 for both nests and lumina, showing their unity. In moderately differentiated adenocarcinoma the lumina, having no anastomosis ($p_1 = 0$), are separated into 439 parts. This defines a state of porosity. In the poorly differentiated type the nests also become separated into 871 parts, expressing their fragmentation. These treatments are of essential importance in comparing adenocarcinoma with borderline or non-carcinomatous lesions.

It has been said by some pathologists including Grundmann (1975) that the microscopic diagnosis of adenocarcinoma should rely not only on dysplasia of individual cells but also on abnormal glandular pattern, an equally important diagnostic marker. To formulate how and to what extent the carcinomatous glands deviate from non-carcinomatous ones is a prerequisite to the establishment of a criterion workable in routine practice. Böhmig (1935, 1937) studied serial sections from well differentiated adenocarcinomas arising in stomach, colon and endometrium. His work is one of few contributions to our knowledge about the present question, but he went no further than pointing out in these tumors some anatomical features were analogous to normal glands. In fact, when an adenocarcinoma consists purely of well differentiated cells, its architecture also simulates ordinary glands by showing more or less connected lumina, while this finding disappears as dedifferentiation of the carcinoma advances. The concept of the structural framework of adenocarcinoma that we have introduced enables us to measure, in various tumors, the grade to which the ordinary structures are perverted or disintegrated. The analysis of the framework is performed by reducing an actual architecture to a set of geometric variables. This effectively describes how carcinoma differs from related lesions, for instance gastric adenomas (see Takahashi and Iwama).

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