

Pathological Characteristics of Gastric Carcinomas in the Very Old

Naoko Inoshita,^{1,2,3,4} Akio Yanagisawa,² Tomio Arai,³ Tomoyuki Kitagawa,² Katsuiku Hirokawa¹ and Yo Kato²

¹Department of Pathology and Immunology, School of Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, ²Department of Pathology, Cancer Institute, 1-37-1 Kami-Ikebukuro, Toshima-ku, Tokyo 170-8455 and ³Department of Pathology, Tokyo Metropolitan Geriatric Hospital, 35-2 Sakae-cho, Itabashi-ku, Tokyo 173-0015

A total of 69 gastric carcinomas of very old people (aged ≥ 85) were collected and pathologically analyzed in comparison with those of young to middle-aged (30–39) and elderly (65–69) people, with special attention to their phase. In the very old, almost all (34/35) carcinomas in the early phase belonged to well-differentiated categories. In the advanced phase, half of them (17/34) were classified into poorly differentiated categories when determined from the predominant pattern, but a well-differentiated pattern almost always coexisted in the superficial site. Thus, the gastric carcinomas in the very old may principally develop as well-differentiated carcinomas which then progress to poorly differentiated carcinomas with time, in contrast to those of the young to middle-aged, most of which emerged from the very early phase as poorly differentiated lesions. The gross features of the carcinomas were also in line with these histological observations. The carcinomas of the elderly showed distinct similarity to those of the very old. The results suggest that poorly differentiated carcinomas of the young to middle-aged and the old may be better classified and analyzed separately in view of the generally recognized etiological (e.g., specifically close causal relationship with environmental factors of the intestinal-type carcinoma of the old) and biological (e.g., practically no tendency for hematogenous metastasis of the diffuse-type carcinoma of the young to middle-aged) differences, although in the General Rules for Gastric Cancer Study of Japan, both are placed in the same category, *por* (*por2*).

Key words: Gastric cancer — Histology — Age — Classification

The incidence of gastric carcinomas in old people has been increasing remarkably in Japan due to the extension of the life span in the general population (averages of 77 years for males and 83 for females in 1996), as well as a retardation in cancer onset.^{1,2)} A similar tendency has also been documented in the United States.³⁾ The consequence is that the treatment modality for malignancies in the very old is now an important clinical issue, since such people are at distinctly higher risk from surgery and/or chemotherapy on the one hand and have only a limited life expectancy on the other hand.⁴⁾ A balanced judgment requires elucidation of the biological character and natural history of carcinomas in elderly people, especially the very old. However, this question has received only limited attention so far.

The present analysis of pathological characteristics of gastric carcinomas in people aged 85 and over was therefore performed, with a comparison of lesions in young to middle-aged (30–39 years) and elderly (65–69 years) populations. The study revealed that the poorly differentiated carcinomas of the very old are principally derived from well-differentiated carcinomas, in contrast to those of the

young to middle-aged, and casts some doubt on the adequacy of the simple traditional dichotomy, i.e., diffuse or intestinal, or well-differentiated or poorly differentiated.

MATERIALS AND METHODS

Patients A total of 69 gastric carcinomas obtained from 57 patients (male/female; 27/30) aged 85 years and over (the very old) were examined. For comparison, 69 lesions from 55 patients (M/F; 31/24) ranging in age between 65 and 69 years (the elderly) and 54 from 51 patients (M/F; 30/21) aged between 30 and 39 years (young to middle-aged) were employed.⁵⁾ Surgical resection was performed for the very old and elderly groups at the Tokyo Metropolitan Geriatric Hospital, Japan, and for the young to middle-aged patients at the Cancer Institute Hospital, Tokyo, in both cases between 1985 and 1994.

In the very old group, there were 8 cases having multiple carcinomas: 5 double, 2 triple and 1 quadruple. Six of the elderly patients had two carcinomas and 1 had nine. In the young to middle-aged group, 3 cases had double carcinomas.

Processing of surgical materials Materials were processed according to the General Rules for Japanese Classification of Gastric Carcinoma.⁶⁾ Briefly, each resected stomach was opened along the greater curvature, placed

⁴ To whom reprint requests should be addressed at the Department of Pathology, Cancer Institute, 1-37-1 Kami-Ikebukuro, Toshima-ku, Tokyo 170-8455.

on a wood board with the mucosa up, tacked with nails and fixed with 10% formalin. When the carcinoma was macroscopically limited to the mucosal or submucosal layer, the whole area including the lesion was serially cut into long strips (5–8 mm in width) and when it was apparently more advanced, several portions including the center of the lesion were examined. These cut materials were paraffin-embedded, sectioned, and stained with hematoxylin and eosin (HE). Macroscopical and histological examinations were performed independently by at least two pathologists: macroscopically, T. A. and N. I. and histologically, T. A., A. Y., Y. K., T. K., and N. I.

Stage classification Subdivision into early and advanced was also made on the basis of depth of invasion, according to the Japanese Classification of Gastric Cancer⁶⁾ and AFIP.⁷⁾ Early gastric carcinoma is defined as a carcinoma for which invasion is confined to the mucosa (epithelium) and submucosa. Advanced gastric carcinomas are those which have invaded into or beyond the muscularis propria.

Macroscopic classification The locations of gastric carcinomas were assigned to one of three regions: the upper one-third, the middle one-third and the lower one-third. When the carcinoma was widespread, the site showing the deepest ulceration or invasion was considered as the origin. Based on the Japanese Classification of Gastric Carcinoma,⁶⁾ early gastric carcinomas were classified into five macroscopic types: protruded type (type I); superficial elevated type (type IIa); flat type (type IIb); superficial depressed type (type IIc); and excavated type (type III). Advanced carcinomas were classified into five types⁶⁾: polypoid or fungating type (type 1); excavating type (type 2); ulcerated and infiltrating type (type 3); infiltrating type (type 4); and non-classifiable (type 5).

Histological classification All the carcinomas were principally classified into either well (well-moderately) differentiated or poorly differentiated type based on the criteria described by Laurén,⁸⁾ Ming,⁹⁾ Nakamura¹⁰⁾ and Esaki *et al.*¹¹⁾

Table I. Histological Types of Gastric Carcinoma and Symbols Used

Dichotomy	
Well-differentiated carcinoma category	<i>pap</i> ; Papillary adenocarcinoma <i>tub</i> ; Tubular adenocarcinoma (<i>tub1</i>) (well-differentiated) (<i>tub2</i>) (moderately differentiated)
Poorly differentiated carcinoma category	<i>por</i> ; Poorly differentiated adenocarcinoma (<i>por1</i>) (solid type) (<i>por2</i>) (non-solid type) <i>sig</i> Signet-ring cell carcinoma

When subclassification was needed, symbol terms *tub1*, *tub2*, and *por* or *sig* of the Japanese Classification of Gastric Cancer⁶⁾ (Table I) were applied for well, moderately and poorly differentiated adenocarcinomas, respectively. Well-differentiated adenocarcinomas (*tub1*) have well-developed glands lined by columnar or cuboidal tumor cells with basally oriented nuclei and variable amounts of intracytoplasmic mucin. Moderately differentiated adenocarcinomas (*tub2*) feature cribriform, fused glandular or microtubular patterns, but their architecture is less well defined. Poorly differentiated adenocarcinomas (*por* and *sig*) are characterized by loss of glandular structure and cell adhesion and/or the appearance of signet-ring cells.

For simplification, data for *tub1* and *tub2* are put together in a well-differentiated category (w), and also *sig* and *por* are grouped together in the poorly differentiated category (p). When *tub1* and/or *tub2* patterns were mixed with *por*, these cases were classified into w>p or w<p categories according to the predominance of the well (*tub1* and *tub2*) and poorly differentiated (*por* and *sig*) elements.

Statistical analysis Student's *t* test and the χ^2 test were used to examine differences between groups.

RESULTS

Locations and macroscopic types Intra-gastric locations of the carcinomas in 3 age groups are summarized in Table II. In the very old group, 49% of carcinomas were located in the lower one-third and only 12% in the upper one-third, in contrast with those of the young to middle-aged group, in which the figures were 26% and 24%, respectively ($P<0.05$).

Findings for the macroscopic types of early carcinomas in the 3 age groups are summarized in Table III. In the very old group, 43% were of protruded (I) or superficial

Table II. Intra-gastric Location of Carcinoma

Age groups in years	Upper third	Middle third	Lower third
30–39 (<i>n</i> =54)	13 (24%)	27 (50%)	14 (26%)
65–69 (<i>n</i> =69)	11 (16%)	33 (48%)	25 (36%)
≥85 (<i>n</i> =69)	8 (12%)	27 (39%)	34 (49%)

Table III. Macroscopic Types of Early Gastric Carcinoma

Age groups in years	I	IIa	IIb	IIc	III
30–39 (<i>n</i> =30)	0	2 (7%)	0	28 (93%)	0
65–69 (<i>n</i> =30)	3 (10%)	2 (7%)	3 (10%)	22 (73%)	0
≥85 (<i>n</i> =35)	2 (6%)	13 (37%)	4 (11%)	16 (46%)	0

elevated type (IIa) and only 46% of superficial depressed type (IIc), whereas the latter accounted for 93% of cases in the young to middle-aged group ($P<0.05$).

The distribution of macroscopic types of advanced carcinomas in the 3 age groups is summarized in Table IV. In the very old group, 44% of carcinomas were type 1 or 2, whereas only 18% were type 4. This is in sharp contrast with the young to middle-aged group, in which only 4% belonged to type 1 or 2 and 54% were type 4, the differences being statistically significant ($P<0.05$).

Differential distribution of histological types of gastric carcinoma by age Well (*tub1*) moderately (*tub2*) and

poorly differentiated (*por* and *sig*) components of a typical case of early carcinoma in the very old showing mixed histological features are illustrated in Fig. 1, a–d. Typical cases of carcinoma in the young to middle-aged, showing signet ring cells, microtubular structure or scirrhous invasion, are illustrated in Fig. 2, a–c.

The histological distribution of carcinomas by age groups and stage is summarized in Table V.

Of the early carcinomas in the very old, 51% (18/35) were well-differentiated. When w>p cases were included, 97% (34/35) belonged to the well-differentiated category, with only 1 w<p and no poorly differentiated lesions. In the advanced carcinomas of the very old, there was a distinct shift to the poorly differentiated categories. But 50% (17/34) of the cases still belonged to the well-differentiated category. It is of note that in almost all the advanced carcinomas (15/17) classified into the poorly differentiated category from the predominant pattern, well-differentiated patterns were detectable in the superficial site. In sharp contrast, only 10% (3/30) of the early carcinomas in the young to middle-aged group was well-differentiated.

Table IV. Macroscopic Types of Advanced Gastric Carcinoma

Age groups in years	1	2	3	4	5
30–39 (n=24)	0	1 (4%)	10 (42%)	13 (54%)	0
65–69 (n=39)	2 (5%)	15 (38%)	12 (31%)	9 (23%)	1 (3%)
≥85 (n=34)	4 (12%)	11 (32%)	13 (38%)	6 (18%)	0

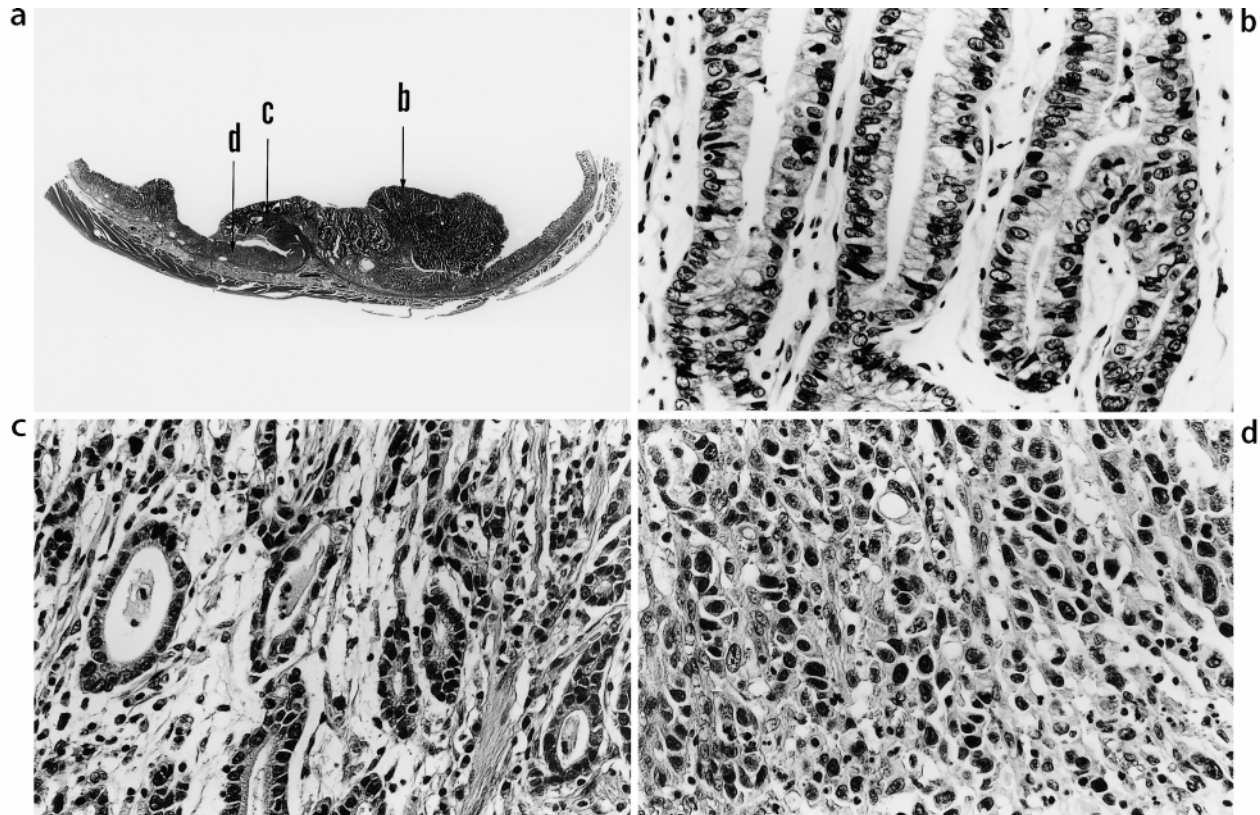


Fig. 1. An early gastric carcinoma in a female aged 93 showing variable histological patterns : a) macroscopical view of a cut section showing intramucosal spread and invasion down to submucosa (HE); b) a site showing well-differentiated features (*tub1*); c) a moderately differentiated area (*tub2*), and d) a poorly differentiated area (HE, $\times 400$).

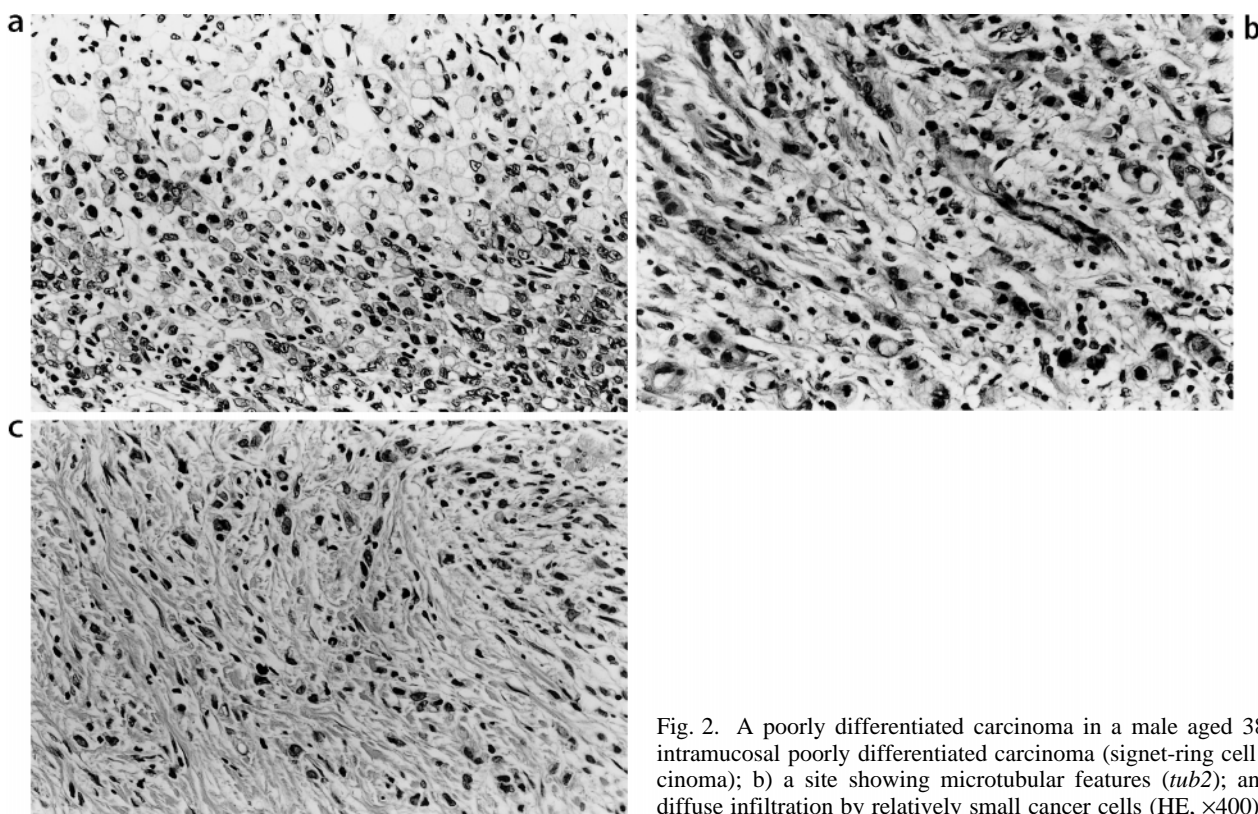


Fig. 2. A poorly differentiated carcinoma in a male aged 38: a) intramucosal poorly differentiated carcinoma (signet-ring cell carcinoma); b) a site showing microtubular features (*tub2*); and c) diffuse infiltration by relatively small cancer cells (HE, ×400).

Table V. Histological Classification of Gastric Carcinomas

Age group in years	Stage	Well-diff.	Mixed type		Poorly diff.
			w>p	w<p	
30–39 n=54 (33/21)	Early	1 (1/0): 3%	2 (2/0): 7%	11 (9/2): 36%	16 (9/7): 54%
	Advanced	0	1 (1/0): 4%	8 (3/5): 33%	15 (8/7): 63%
65–69 n=69 (43/26)	Early	15 (12/3): 50%	9 (7/2): 30%	3 (1/2): 10%	3 (1/2): 10%
	Advanced	1 (1/0): 3%	12 (9/3): 31%	18 (10/8): 46%	8 (2/6): 20%
≥85 n=69 (32/37)	Early	18 (10/8): 51%	16 (7/9): 46%	1 (0/1): 3%	0
	Advanced	3 (2/1): 9%	14 (7/7): 41%	15 (5/10): 44%	2 (1/1): 6%

Numbers in parenthesis: male/female ratio.

ated and more than half (16/30) of all lesions, most being intramucosal carcinoma, belonged to the poorly differentiated category.

The results of a detailed study of the histological grade of the well-differentiated component in mixed carcinomas in the early stage (“mixed type” in Table V) are given in Fig. 3; in the very old group, 8 cases (47%) were *tub1*, 6 (35%) were *tub1+tub2*, and 3 (18%) were *tub2*. In con-

trast, in the young to middle-aged group, 9 cases (75%) were *tub2*, with only 1 (8%) *tub1* and 2 (17%) *tub1+tub2*.

Some histological differences were also noted between *tub2* of the very old and the young to middle-aged groups: in the former, they principally showed irregular glands or cribriform to acinar structures composed of large cuboidal cells (Fig. 1c), whereas the *tub2* component in the young to middle-aged group mainly exhibited fused

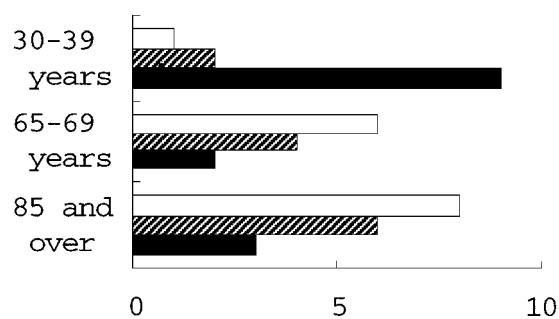


Fig. 3. Subclassification of mixed carcinomas in the early stage by histological grade of the well-differentiated component. □ *por+tub1*, ▨ *por+tub1+tub2*, ■ *por+tub2*.

glandular or irregular microtubular structures (Fig. 2b) consisting of relatively small cells with a remarkable desmoplastic reaction in invasion sites (Fig. 2c). The macroscopic and histological features of the carcinomas in the elderly group were intermediate between those of the very old and the young to middle-aged groups, but with greater similarities to the former.

One or two flat adenoma(s) coexisted with a carcinoma in 4 cases in the very old and 1 in the elderly group. But they were all separate lesions and there was no case suggesting an adenoma-carcinoma sequence.

DISCUSSION

The present investigation clearly suggests that gastric carcinomas in very old people principally develop as well-differentiated carcinomas which may then progress to poorly differentiated carcinomas with time, in contrast with those of the young to middle-aged, which mostly emerge from the early stage as poorly differentiated lesions. Evidence supporting these conclusions includes: 1) an absence of pure *por* cases in 24 early cancers in the very old; 2) an almost ubiquitous (32/34) coexistence of well-differentiated patterns in *por*-predominant advanced carcinomas in this group; and 3) a very high rate (27/30) of *por* or *por*-predominant carcinomas in the young to middle-aged even at an early stage. The gross features of the carcinomas were also in line with these histological observations, with a relative predominance of type I and IIa early and type 1 and 2 advanced carcinomas, respectively, in the very old. In contrast, type IIc early and type 3 and 4 advanced carcinomas were very frequent in the young to middle-aged.⁷⁾

To our knowledge, this is the first detailed study of pathological differences in gastric cancers in the very old in comparison with those in young to middle-aged individuals. The histological distribution of the carcinomas of

the elderly group was intermediate between those of the very old and the young to middle-aged groups, but with distinct similarity to the former. Thus, the present study of the carcinomas of the very old has proven helpful for clarifying the characteristics of gastric carcinomas of the old in general.

Many reports have indicated that well-differentiated carcinomas are more common in elderly people than in the young to middle-aged.¹²⁻¹⁵⁾ In these previous studies, however, early and advanced carcinomas were not examined separately, and histological differences between respective "well-differentiated types" and "poorly differentiated types" were not carefully taken into consideration, since the histological type of a carcinoma was determined simply by the predominance of well or poorly differentiated patterns. Consequently, differences in histological patterns and especially the well to poorly differentiated carcinoma sequence in aged people seen in the present study were not clearly recognized. The considerable inconsistencies among data^{12, 14, 16)} concerning the w/p ratio of carcinomas developing in old people may be explained on the same basis.

Common-type gastric carcinomas have traditionally been classified into intestinal or diffuse (Laurén⁸⁾), expanding or infiltrative (Ming⁹⁾), or well-differentiated or poorly differentiated types (Nakamura and Sugano^{10, 17, 18)}), and there seems to be a consensus that the two types in each classification roughly overlap.^{7, 17-19)} This dichotomy is important since intestinal (expanding, well-differentiated) carcinomas are considered to have a close relationship with environmental causal factors, whereas diffuse (infiltrating, poorly differentiated) lesions show only a loose connection.^{17, 19-21)} Furthermore, their developmental pathways have recently been suggested to differ at the genetic level,^{22, 23)} and in addition, the former often produces hematogenous metastasis to the liver, the latter practically does not. It should be noted, however, that Laurén's classification was derived from observations of advanced cancers, whereas Nakamura and Sugano's concept came from an analysis of early carcinomas.^{8, 10)} The present results are quite in concert with those of Nakamura and Sugano concerning early carcinomas. As to advanced lesions, however, the observations cast some doubt on the traditional dichotomy, since well-differentiated carcinomas in aged people were found to shift to poorly differentiated ones so long as the histological category was determined from the predominant pattern. In the future, we suggest it would be better to classify poorly differentiated carcinomas of aged people and diffuse-type carcinomas of the young to middle-aged into different categories, especially for etiological, genetical and biological analyses, the last item covering parameters such as proliferative activity, metastatic mode and chemo- or radiosensitivity. It should be possible to distinguish between the

two groups on the basis of their gross and histological features, apart from the patient's age, as shown in this study.

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