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Biological Differences Between Polypoid and Nonpolypoid Growth Types of Colorectal Cancer

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Background- Two distinct morphologic types of colorectal cancer have been described in recent studies: polypoid growth type (PG-type) and nonpolypoid growth type (NPG-type).

Materials and Methods- We investigated possible biological and clinical differences between 37 PG-type and 156 NPG-type cancers using both univariate and multivariate analyses (logistic and Cox regression models).

Results- Unlike NPG-type cancers, PG-type cancers had a high proportion of well-differentiated adenocarcinoma cells, a high likelihood of being early colorectal cancers (carcinoma *in situ* and cancer invades submucosa), and a low frequency of lymph node metastasis. On average, such PG-type cancers also carried a better prognosis than NPG-type cancers (P=0.01). In particular, PG-type cancer patients with stage IV tumors had a better prognosis than NPG-type cancer patients (P=0.02). In fact, after performing a Cox regression analysis, we found that colorectal cancer growth type is an independent prognostic variable, separate from histologic type or stage.

Conclusions- PG-type colorectal cancer is less aggressive and has a favorable prognosis compared to NPG-type cancer.

Key Words: colorectal cancer; polypoid growth; PG-type; nonpolypoid growth; NPG-type

Introduction

Colorectal cancer, much like other cancers, has a prognosis that depends significantly upon the staging of the tumor at the time of diagnosis and treatment. Fortunately, recent advances in endoscopical technology for colorectal tumors have allowed for the detection of increasing numbers of small, early colorectal cancers (tumors in which invasion is limited to but no deeper than the submucosa)[1)]. The utilization of such new technology has brought an enhanced understanding of the underlying disease process. Specifically, careful investigation of early colorectal cancers, which were resected endoscopically or surgically, has revealed two different morphological types and suggested the existence of alternative biological and molecular pathways leading to the development of colorectal cancers.

Pathological distinctions further underscore the notion of two tumor growth patterns, as flat-type early colorectal cancer both appears and behaves differently than polypoid early cancers[1,2)]. Namely, such flat-type early cancers have a low incidence of accompanying adenomas and often invade the submucosal layer when they are small in size[2,3)]. In contrast, pedunculated or sessile polypoid growth, which is seen in the majority of early cancers, demonstrate carcinoma within adenomatous tissue by histology[4,5)]. Based upon these observations, some researchers postulate that polypoid early cancers may originate from protruding adenomas, whereas flat type early cancers may develop de novo[6,7)] or from flat adenomas[8,9)].

Shimoda et al.[10)] classifies colorectal cancers into two types based upon growth patterns: polypoid growth (PG-type) and nonpolypoid growth (NPG-type) cancers. The gross and histologic growth patterns seen in NPG-type early cancers are identical to those seen in NPG-type advanced cancers (tumors in which invasion extended into the muscularis propria and deeper tissues)[10)]. In keeping with such findings, NPG-type early cancers have received increasingly greater attention as a likely precursor

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candidate for advanced colorectal cancer. Recently, further evidence for the legitimacy of Shimoda s classification system has come as studies have described differences in the cellular and genetic features of PG-type and NPG-type cancers, as determined by molecular analyses. The cellular and genetic differences include differing incidences of K-*ras* mutation[9,11-13], cellular proliferation activities[14], and distinct chromosomal aberrations[15,16].

Collectively, these observations suggest that separate genetic pathways for tumor progression may exist for PG-type and NPG-type colorectal cancers. Despite the advancements in research and understanding, the biologically and clinically relevant differences between the two tumor morphologies has yet to be fully elucidated. Even in the report of Shimoda et al.[10], it was not enough to discuss the relationship between the clinicopathological factors or patient prognosis and the tumor growth patterns, ie. PG-type and NPG-type. We hypothesize that such morphologic differences between PG-type and NPG-type cancers may reflect underlying differences in biological characteristics as well as in the cellular or genetic features of the cancer cells themselves. Therefore, the present study was designed to clarify the different biological characteristics possessed by PG-type and NPG-type colorectal cancers, as assessed by clinicopathological variables using univariate and multivariate analysis.

Materials and Methods

A total of 193 patients with primary colorectal cancers who underwent surgical resection at Nagasaki University Hospital between January 1986 and December 1993 were studied. The exclusion criteria for this study were the following: more than one cancer of the colon and rectum, polyposis coli, a tumor which directly invades other organs or structures and/or perforates visceral peritoneum, or macroscopic-type cancers such as diffusely infiltrating and unclassified types. American Joint Committee on Cancer Classification and Stage groupings were used for tumor assessment[17]. All colorectal carcinoma specimens were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin. After staining, histologic types were determined by two pathologists according to the World Health Organization International Histological Classification of Tumours[18]. Additionally, all routine slides were carefully screened to identify venous and lymphatic invasion when tumor tissue was seen within vein and lymph-vessel, respectively.

All patients underwent standard follow-up examinations, including laboratory testing every 3 months. Chest roentgenogram, computed tomography, abdominal ultrasound scanning, and colonoscopy were performed annually. The median length duration of follow-up time was 1827 days (range: 108 - 3861 days). Of the 193 patients, 118 patients are alive at the time of this writing (July, 1999). Recurrence of colorectal cancer followed by death occurred in 59 patients, and 16 patients died of a different disease with no evidence of colorectal tumor. The data on patients who died of causes other than colorectal cancer were censored in the statistical analysis[19].

Tumor growth pattern

According to Shimoda s classification[10], all tumors were classified into two groups based on morphologic pattern of tumor growth as follows: (1) polypoid growth type (PG-type) cancer is characterized by an exophytic growth pattern and a mucous membrane immediately adjacent to the edge of the colorectal carcinoma tissue is covered by everted carcinoma tissue (Fig. 1), and (2) nonpolypoid growth type (NPG-type) cancer primarily is characterized by massive invasion into the deeper tissue and a mucous membrane imme-

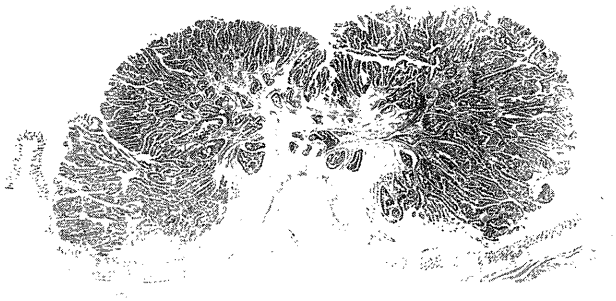

Figure 1. Microscopic profile of PG-type colorectal cancer (Hematoxylin and eosin; x1.0).

Figure 2. Microscopic profile of NPG-type colorectal cancer (Hematoxylin and eosin; x1.0).

diately adjacent to the edge of carcinoma tissue is free of carcinoma tissue (Fig. 2).

Statistical analysis

Statistical analyses were performed using SAS statistical-analysis software (SAS Institute, Cary, North Carolina, USA). Specifically, univariate analyses were conducted as follows: categorical data were analyzed by chi-square or Fisher's exact probability tests; continuous data were analyzed using the unpaired t-test; survival analyses were performed using the Kaplan-Meier method[20], and differences between the curves were tested using the log-rank test[21].

In order to conduct multivariate analyses, we employed both the logistic regression model[22,23] and the Cox proportional hazards model[24]. The logistic regression analysis was chosen to study the predictive value of risk factors because the outcome variable was binary, such as NPG-type vs. PG-type[23]. By means of univariate analysis, potentially predictive variables were identified at a significance level of $P < 0.25$, and these variables were then used for logistic regression multivariate analysis[22]. The odds were expressed as the ratio of NPG-type to that of PG-type for a given value of an independent variable. Factors related to survival were also analyzed with the Cox proportional hazards regression model[24]. The tumor growth patterns (PG-type and NPG-type) were compared to other prognostic variables, including stage and histologic type that are generally used in colorectal cancer patient management and well-supported in the literature[17]. All tests were two-tailed and a P value of less than 0.05 was considered significant.

Results

Of the 193 colorectal cancers, 37 (19.2%) were classified as PG-type cancers and 156 (80.8%) were classified as NPG-type cancers.

Comparison of the clinicopathologic features of the PG-type and the NPG-type cancers

There were no differences in age, sex, tumor location, tumor size, M factor, lymphatic involvement, or venous involvement between the PG-type and the NPG-type cancers (Table 1). However, in contrast to NPG-type cancer, PG-type cancer had a high proportion of well-differentiated adenocarcinoma cells, a high ratio of Tis/T1 tumors ($P=0.001$ and $P=0.001$, respectively),

Table 1. Clinicopathological features of colorectal cancers according to tumor growth patterns.

Variable	No. of Cancers (%)		*P* value
	PG-type cancer[a] (n=37)	NPG-type cancer[a] (n=156)	
Age[b] (years)	65.3 ± 10.5	62.4 ± 11.7	0.17
Sex			0.71
Male	21 (56.8)	94 (60.3)	
Female	16 (43.2)	62 (39.7)	
Tumor location			0.45
Colon	24 (64.9)	88 (56.4)	
Rectum	13 (35.1)	68 (43.6)	
Tumor size[b] (cm)	5.2 ± 2.1	5.0 ± 1.8	0.52
Histologic type			0.001
Well differentiated	20 (54.1)	33 (21.1)	
Moderately differentiated	13 (35.1)	112 (71.8)	
Poorly differentiated/ Mucinous	4 (10.8)	11 (7.1)	
T			0.001
Tis/T1	10 (27.0)	3 (1.9)	
T2	4 (10.8)	16 (10.3)	
T3	23 (62.2)	137 (87.8)	
N			0.002
N0	29 (78.4)	79 (50.6)	
N1/N2	8 (21.6)	77 (49.4)	
M			0.75
M0	33 (89.2)	142 (91.0)	
M1	4 (10.8)	14 (9.0)	
Lymphatic involvement			0.40
Absent	11 (29.7)	36 (23.1)	
Present	26 (70.3)	120 (76.9)	
Venous involvement			0.66
Absent	30 (81.1)	118 (75.6)	
Present	7 (18.9)	38 (24.4)	
Stage			0.001
I	12 (32.4)	12 (7.7)	
II	15 (40.5)	66 (42.3)	
III	6 (16.2)	64 (41.0)	
IV	4 (10.8)	14 (9.0)	

[a] PG, Polypoid growth; NPG, Nonpolypoid growth.

[b] Age and tumor size were expressed as mean values ± standard deviations.

and a low frequency of lymph node metastasis (P =0.002). PG-type cancers were also, on average, at a less advanced stage than the NPG-type cancers (P=0.001).

Patient survival and tumor growth patterns, NPG-versus-PG-type

Among the patients included in this study, there was a significant difference between the survival of those with PG-type and NPG-type cancers, in that PG-type cancer patients had a better prognosis (P=0.01). In the patients with stage I/II or III tumors, there was no difference in the survival between PG-type and NPG-type cancer, although PG-type cancer patients with stage IV tumors had a better prognosis than NPG-type cancer patients (P=0.02) (Fig. 3). Of four PG-type cancer patients with stage IV tumors, three patients (whose tumors were T3N0M1, T3N0M1, and T3N1M1) who underwent surgical resection for both primary colorectal tumors and synchronous liver or lung metastases, had a long duration of survival after surgery (2026, 2126, and 2018 days). However, one patient (T3N2M1) who had unresectable metastases in the liver, adrenal gland, and lung, died at 557 days after surgery.

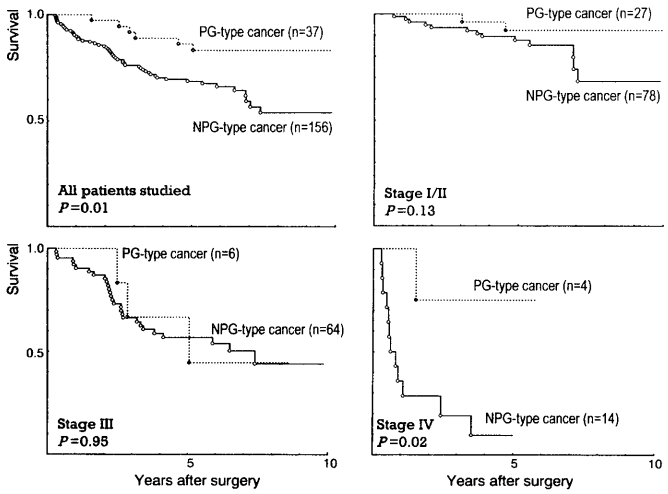

Figure 3. Survival curves for two groups of patients with PG-type and NPG-type colorectal cancer. Among all of the patients studied, there was a significant difference between the survivals of PG-type and NPG-type cancer patients, in that PG-type cancer patients had a better prognosis (P=0.01). In the patients with stage I/II or III tumors, there was no difference in the survival between PG-type and NPG-type cancer, although PG-type cancer patients with stage IV tumors had a better prognosis than NPG-type cancer patients (P=0.02).

Comparison of patterns of initial recurrence after curative surgery between two tumor growth patterns, NPG-versus-PG-type

Of the 34 PG-type cancer patients who underwent curative resection, 6 patients developed tumor recurrence after surgery, of which 5 (5/6, 83.3%) were hematogenous metastases and 1 was a local recurrence within the pelvis. Of the 138 NPG type-cancer patients who underwent curative resections, 40 patients developed tumor recurrence after surgery. Of these 40 cases, 19 (19/40, 47.5%) were hematogenous metastases, 14 were local/lymph node recurrences, 4 were peritoneal disseminations, and 4 were unknown recurrences (one patient developed both liver and peritoneal metastasis). A ratio of hematogenous metastases to tumor recurrences after curative surgery in PG-type cancer patients was higher that that in NPG-type cancer patients, although the difference was not significant (83.3% vs 47.5%, respectively, P=0.18).

Predictive value of tumor growth patterns, NPG-versus-PG-type

In order to determine the independent factors that were related to tumor growth patterns for colorectal cancer (i.e. NPG-versus-PG-type), logistic regression analysis was conducted. Four factors (age, histologic type, T, N), which were identified at a significance level of $P<0.25$ by means of univariate analysis (Table 1), were included in this analysis. Of these studied factors, three variables -- namely histologic, T factor and N factor -- were found to be independently related to tumor growth patterns (Table 2). That is, NPG-type cancer was characterized by a high proportion of moderately-differentiated adenocarcinoma cells, a high proportion of T2 and T3 tumors, and a high

Table 2. Results of multivariate analysis using the logistic regression model for tumor growth pattern of colorectal cancer.

Variable	Odds ratio	(95% Confidence interval)
Age		
≥63 years	1.00	
<63 years	1.82	(0.76-4.35)
Histologic type		
Well differentiated	1.00	
Moderately differentiated	3.06	(1.20-7.82)
Poorly differentiated/ Mucinous	0.85	(0.20-3.59)
T		
Tis/T1	1.00	
T2	10.86	(1.68-70.01)
T3	12.83	(2.71-60.72)
N		
N0	1.00	
N1/N2	3.46	(1.32-9.06)

frequency of lymph node metastasis (odds ratio = 3.06, 10.86, 12.83, and 3.46, respectively).

Prognostic value of tumor growth patterns, NPG-versus-PG-type

In order to clarify the independent predictive value of each clinicopathological variable for survival after surgery, Cox's regression analysis was performed. In this case, three factors (tumor growth pattern, histologic type, stage) were included. The tumor growth pattern (i.e. NPG-type or PG-type) proved to be independently associated with patient survival following surgery, separate from histologic type or stage. That is, the patients who had NPG-type cancer had a worse survival outcome compared with patients who had PG-type cancer (hazard ratio = 3.13) (Table 3).

Table 3. Results of multivariate analysis using Cox's proportional hazard regression model.

Variable	Hazard ratio	(95% Confidence interval)
Tumor growth pattern		
PG-type[a]	1.00	
NPG-type[a]	3.13	(1.25-7.83)
Histologic type		
Well differentiated	1.00	
Moderately differentiated	1.14	(0.59-2.21)
Poorly differentiated/ Mucinous	3.25	(1.20-8.77)
Stage		
I/II	1.00	
III	3.80	(2.02-7.13)
IV	19.12	(8.54-42.78)

[a] PG, Polypoid growth; NPG, Nonpolypoid growth.

Discussion

We previously reported the differential expression of sialyl Tn antigen between polypoid and flat-type early colorectal cancers[25]. Sialyl Tn is a tumor-specific carbohydrate antigen which is strongly expressed in a large number of colorectal cancers, while it is not expressed at all in normal mucosa[26]. This antigen might be useful as an intermediate end point biomaker of transformation from normal epithelium to adenomas with a potential for malignancy[27]. Specifically, Sialyl Tn antigen was expressed in 17 (54.9%) of 31 polypoid early cancers and 4 (14.9%) of 27 flat-type early cancers, and this difference was statistically significant[25]. Although the microscopic features of these cancers were similar, such characteristics of the cancer cells themselves in polypoid and flat-type early cancers were different[25]. Distinct cellular or genetic features defined by molecular analysis with respect to the growth pattern classification involving PG-type and NPG-type cancers have been reported. Compared to PG-type cancers, NPG-type cancers possess a low incidence of K-*ras* mutations[9,11-13], different cellular proliferation activity[14], and different numerical chromosomal aberrations[15,16]. Based upon these reports, there may be at least two different pathways in colorectal carcinogenesis and tumor progression, and it may be important to recognize the existence of a NPG-type cancer pathway that is quite different from the PG-type cancer pathway[9].

Besides the potential clinical, cellular, and molecular reasons for distinction among PG-type and NPG-type cancers, biological features supply an added basis for separation. The current study reveals that NPG-type cancer have a higher proportion of moderately-differentiated adenocarcinoma cells, a higher ratio of T2/T3 tumors, and a higher frequency of lymph node metastasis than PG-type cancers, as shown by univariate and multivariate (logistic regression) analyses. Yanagida et al.'s work[28] provides more evidence elucidating the fundamental differences between the two growth patterns as he demonstrates that NPG-type cancers are smaller in size, found in younger age, and more commonly have lymph node metastasis than PG-type cancers. Shimoda et al.[10] also reported that lymphatic and venous permeation in NPG-type early cancers was detected more often than in PG-type cancers. Although NPG-type cancers are smaller than those of PG-type, marked submucosal invasion, lymphatic spread, and venous permeation of cancer cells were observed in NPG-type cancers[10]. Collectively, these data suggest that many NPG-type cancers may exhibit tumor aggressiveness not seen in most PG-type cancers - a behavior that may explain their poorer outcomes. In our study, the obtained data did reinforce this idea, as a significant difference between the survival of PG-type and NPG-type cancer patients was evident, with NPG-type cancer patients having a poorer prognosis. Furthermore, the multivariate analysis using Cox regression analysis proved that tumor growth pattern (i.e. NPG-type or PG-type) is an independent prognostic variable, in addition to and separate from histologic type and stage.

Within our study group, PG-type colorectal cancer represented 19.2% of the 193 cancers studied, comprising 77.0% of 13 early colorectal cancers and 15.0% of 180 advanced cancers. Shimoda et al.[10] also reported the similar incidence of PG-type cancer. Why is there a difference in the proportion of PG-type cancer between the early and advanced colorectal cancer? There is an idea that NPG-type early cancer may be the

major precursor for advanced colorectal cancer, while PG-type early cancer, possessing less tumor aggressiveness and slower progression, may be the minor precursor candidate for advanced cancer[10]. On the other hand, Matsui et al.[29] recently reported that, to some extent, PG-type early colorectal cancer develops into NPG-type advanced cancer, based on a retrospective analysis of barium enema studies. It is speculated that some of the PG-type early cancers may develop morphologically into NPG-type advanced cancers. This phenomenon may be associated with necrosis and destruction of the polypoid-type cancer tissues correlating with increased malignant behavior, such as advanced invasion or deterioration of histologic differentiation.

Thus, it remains unclear which growth type of early colorectal cancer may be the major precursor of advanced colorectal cancer. However, in the current study, at least two distinct growth patterns (PG-type or NPG-type) are characterized by biological and clinical features. In contrast to the NPG-type cancers, the PG-type cancers seem to be characterized by less tumor aggressiveness and a favorable prognosis. In addition, tumor growth pattern is not correlated with the presence or absence of distant metastasis (M factor). The PG-type cancers with synchronous hematogenous metastases (liver or lung), which are concurrently resected with the primary tumors, seem to have a favorable prognosis. Furthermore, it seems that the PG-type cancer has a tendency to develop hematogenous metastases after curative surgery, compared to the NPG-type cancer. Based upon these findings, we think that an aggressive surgical resection for the hematogenous metastases from the PG-type cancer, which has a high proportion of well-differentiated cells and a low frequency of lymph node metastasis, may be recommended.

On the other hand, the NPG-type cancers seem to be characterized by more tumor aggressiveness and a worse prognosis. The detection for early-staged NPG-type cancers, as well as early-staged PG-type cancers, is essential for curing colorectal cancer. Therefore, we feel that increased screening must be performed in order to detect early-staged NPG-type cancers, in recognition of the fact that such NPG-type cancers may be often overlooked by means of colonoscopy or a barium enema study, given that NPG-type early cancers are generally small and have flat-typed shapes[2,10].

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