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Early Colorectal Cancer with Special Reference to the Superficial Nonpolypoid Type from a Histopathologic Point of View

Yoichi Ajioka, M.D., Ph.D., Hidenobu Watanabe, M.D., Ph.D., Shinsuke Kazama, M.D., Hideki Hashidate, M.D., Junji Yokoyama, M.D., Satoshi Yamada, M.D., Hideya Takaku, M.D., Ken Nishikura, M.D.

1st Department of Pathology, School of Medicine, Niigata University, 757-1 Asahimachi-dori, Niigata City, Japan

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Abstract. The incidence and histopathologic characteristics of nonpolypoid (superficial type) early colorectal carcinomas were studied and compared with those of the polypoid type. The superficial type was subclassified as elevated (type IIa), type IIa with central depression (type IIa+IIc), plain (type IIb), depressed (type IIc), and IIc with marginal elevation (type IIc+IIa). The superficial type comprised 22% and 27% of intramucosal and submucosal carcinomas, respectively. Pure type IIb was not found, and there were only three pure type IIc lesions. Type IIa+IIc and IIc+IIa (and IIc) showed a significantly higher rate of submucosal invasion among the small tumors (59% and 71% less than 20 mm, respectively) compared to the polypoid type; type IIa showed no significant difference. The incidence of lymph node metastasis among submucosal carcinomas showed no significant difference between the superficial type and the polypoid type. About 64% and 52% of type IIa and IIa+IIc tumors accompanied residual adenoma, suggesting that they originated from small, flat adenomas through the adenoma–carcinoma sequence, whereas type IIc+IIa (and IIc) did not have an adenomatous component, implying that they arose de novo or originated through an adenoma–carcinoma sequence at a smaller size than the type IIa and IIa+IIc lesions. Superficial-type early colorectal carcinomas are not rare, and they are not uniform in nature. Rapid growth and invasion to the submucosa is characteristic of superficial-type lesions with a central depression, and only superficial depressed (type IIc+IIa, IIc) lesions can arise de novo. Although they grow rapidly to invade the submucosa, it cannot be said that they show more aggressive behavior than the polypoid type.

Attention has been focused on nonpolypoid (superficial) type early colorectal cancers because of an increase in their number being reported [1–5]. Particularly in Japan, they are thought to arise de novo [1, 3, 6–8], show rapid growth and aggressive behavior [3, 9, 10], and play an important role in the developmental process of colorectal carcinoma [7, 11, 12]. Most reports on superficial-type early colorectal cancer have been presented and analyzed by clinicians or from the clinical viewpoint; only a few systemic large-scale studies have been done from a pathology viewpoint [11, 13]. In this paper we demonstrate the histopathologic characteristics of nonpolypoid (superficial) type early colorectal cancers found in Japanese patients and compare them with their polypoid counterparts.

Correspondence to: Y. Ajioka, M.D., Ph.D., e-mail: ajioka@med.niigatau.ac.jp

Materials and Methods

Our material consisted of 1057 early colorectal carcinomas in our surgical pathology files from 1980 to 1998. Of 1057 lesions, 521 (49%) were found clinically and were surgically resected; the rest ($n = 536$) were found by macroscopic observation of the colorectum resected because of advanced carcinoma or other early colorectal carcinoma. Patients with a family history or clinical features contributory to hereditary colorectal cancers and cancers complicating inflammatory bowel disease were excluded. Each lesion was fixed in 10% formalin; and after careful observation with the naked eye, the entire lesion was cut into stepwise sections and stained with hematoxylin and eosin (H&E). All sections were examined histologically.

Early colorectal carcinoma was defined as adenocarcinoma limited to the mucosa or submucosa [14]. The term "intramucosal carcinoma" was used for cancers limited to the mucosa, and cancers invading the submucosa were termed "submucosal carcinomas." The histologic diagnosis and typing of the adenocarcinoma was carried out according to the General Rules for Clinical and Pathological Studies on the Colon, Rectum and Anus set forth by the Japanese Society for Cancer of the Colon and Rectum [15]. Briefly, carcinoma was diagnosed on the basis of cytologic and structural atypia (not only by its invasion of the lamina propria or submucosa). Consequently, some of our "intramucosal carcinomas" would be diagnosed as "adenoma with severe dysplasia" by the World Health Organization (WHO) classification [16]. Histology was classified as well, moderately, or poorly differentiated based on the structural atypia of the carcinoma [15].

Macroscopic types were classified as polypoid (type I) or superficial (nonpolypoid) (type II) [15] based on the height of the lesion compared to the surrounding normal mucosa [17]. The polypoid type (type I) was defined as having a height of more than 3 mm and being pedunculated or sessile; the superficial type was 3 mm or less. For intramucosal lesions (of surgically resected material), a macroscopic height of 3 mm almost always corresponds to a mucosal thickness twice that of the surrounding normal mucosa [18]. The superficial type (type II) was further subclassified into elevated (type IIa) (Fig. 1) with a flat or hemispheric surface,

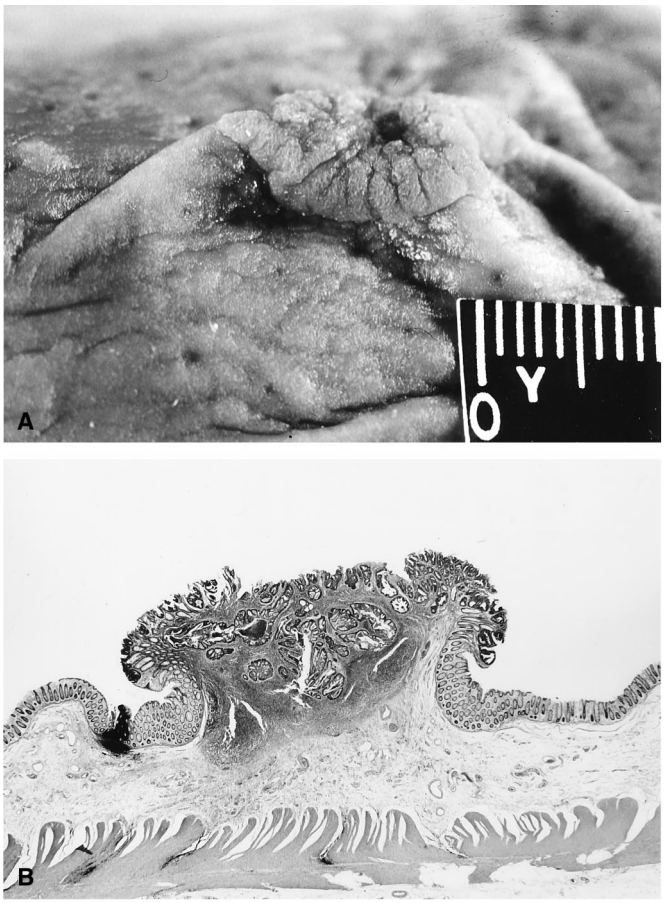

Fig. 1. Superficial elevated type (type IIa) of colorectal carcinoma (CRC) measuring 15 × 10 mm. **A.** Lateral view of the lesion showing slight elevation with flat and focally slightly concaved surface. **B.** Whole-mount view of the representative cut section. Carcinoma was massively invading the submucosa. (×3.3)

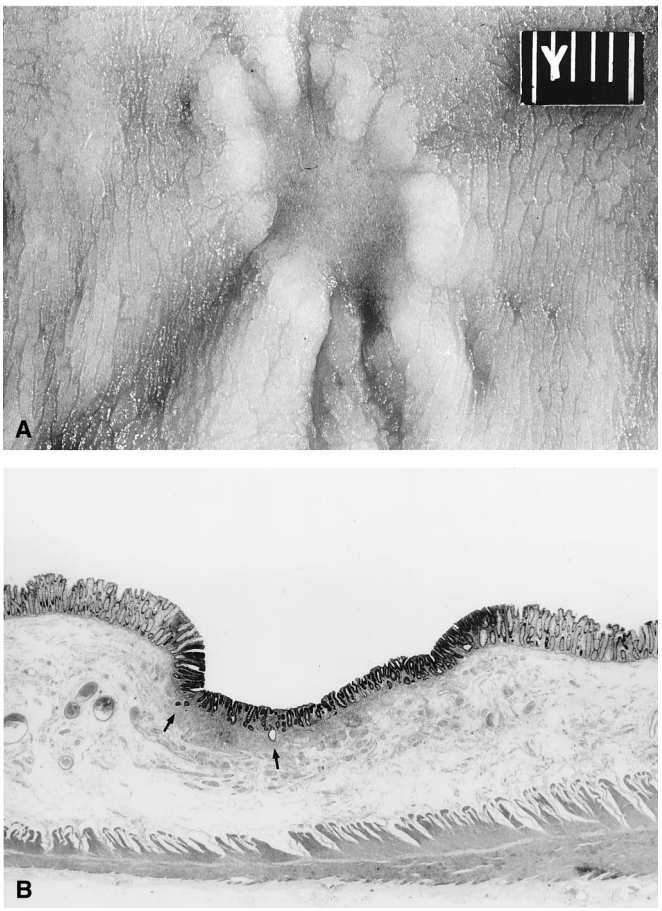

Fig. 2. Superficial depressed type of CRC with marginal slight elevation (type IIc+IIa) measuring 18 × 13 mm. **A.** Depression is clearly demarcated and surrounded by an irregular margin with slight elevation. **B.** Whole-mount view of the representative cut section. Carcinoma was almost confined to the mucosa, with a few minute foci invading the submucosa (arrow). The depression was formed because of the reduced thickness of the neoplastic mucosa. (×3.3)

plain (type IIb), or depressed (type IIc). Type IIa with a central depression was classified as type IIa+IIc; and type IIc surrounded by a type IIa elevated margin was classified as type IIc+IIa (Figs. 2, 3).

Results

The histopathologic characteristics of superficial (nonpolypoid) type early colorectal carcinoma are summarized and compared with the polypoid type in Table 1. The residual adenoma was investigated for the presence of intramucosal carcinoma. Lymph nodal metastasis was sought in 166 submucosal carcinomas (with no advanced carcinoma) that had been subjected to classic surgery including removal of regional lymph nodes.

The superficial type comprised 22% and 27% of all intramucosal and submucosal carcinomas, respectively. Type IIc was grouped with type IIc+IIa, as there were only two lesions of pure depressed type. No pure type IIb lesion was found in our material; these lesions were associated with type IIc (two intramucosal and one submucosal) and were grouped with the type IIc+IIa lesions as well.

Compared to the polypoid type, the superficial type was characterized by a small size (12.6 vs. 21.9 mm for intramucosal carcinomas and 14.2 vs. 24.6 mm for submucosal carcinomas) ($p < 0.001$), frequent invasion to the submucosa (44% vs. 38%) (borderline, $p = 0.058$), and a low rate of accompanying residual adenoma (56% vs. 85%) ($p < 0.001$). These characteristics, excluding the size, were not uniform among superficial subtypes. Type IIa was less frequently submucosal carcinoma among the three subtypes, and no significant difference was found between the polypoid types. Types IIa+IIc and IIc+IIa lesions were similar in size and had a high rate of submucosal invasion, but the rate of residual adenoma differed between the two subtypes. Although statistically significant when compared with the polypoid type, more than 50% of type IIa+IIc and IIa lesions had residual adenoma, whereas none of type IIc+IIa lesions did so (0/13). There were no significant differences between the superficial and polypoid types in terms of the histologic grade of the carcinoma or the rate of lymph node metastasis.

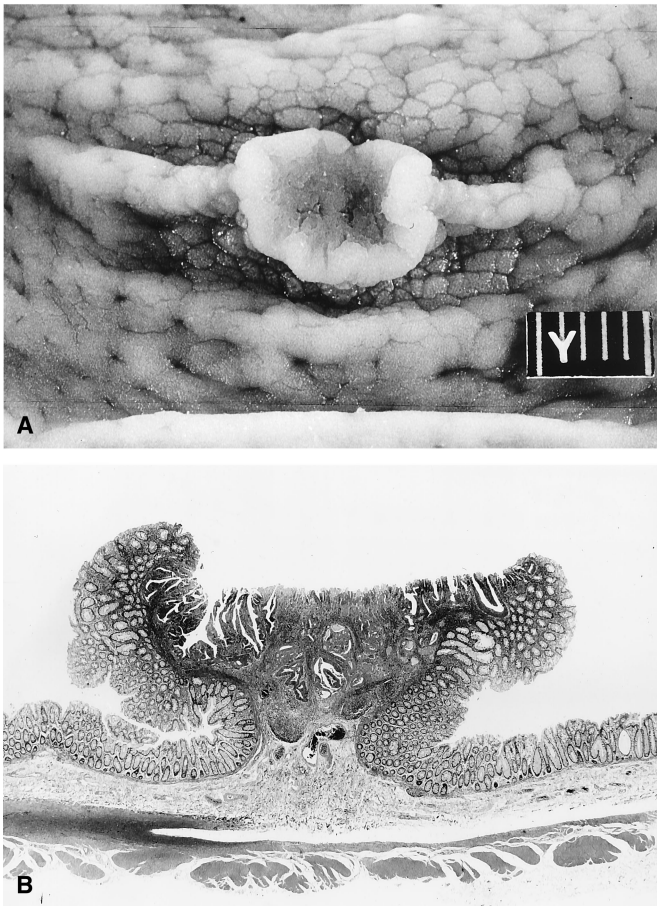

Fig. 3. Superficial depressed type of CRC with slight elevation of the margin (type IIc+IIa) measuring 10 × 8 mm. **A.** Depression is entirely surrounded by a slightly elevated margin. **B.** Whole-mount view of a representative cut section. Center of the lesion is ulcerated or eroded due to massive invasion of carcinoma into the submucosa. The elevated margin consists of surrounding nonneoplastic mucosa that is pulled up by the cancer mass. (×3.3)

Discussion

The incidence of superficial-type early colorectal carcinoma is rare in Western countries compared to that in Japan [19, 20]. This discrepancy between Japan and Western countries may be partly explained by differences in the diagnostic criteria used by Japanese and Western pathologists. Japanese pathologists diagnose carcinoma on the basis of cytologic and structural atypia, not only by its invasion into the lamina propria or submucosa. Consequently, some Japanese superficial-type intramucosal carcinomas (those limited to the mucosa) would be diagnosed as "adenoma with severe dysplasia" by Western pathologists, who consider the presence of evident invasion into the submucosal layer mandatory for a diagnosis of carcinoma [19]. However, if we confine our discussion to "submucosal carcinomas" (those invading the submucosa), the incidence of the superficial type ranged from 32% to 41% [21–23] in earlier studies and was 27% (112/414) in the present series, indicating that superficial-type carcinoma is not rare.

It has been stressed that the clinical importance of superficial-type early colorectal carcinoma is the high rate of submucosal invasion by *small* tumors compared to the polypoid type [2, 3, 7, 23]. This rapid growth to the submucosa is characteristic of the superficial type lesion with a central depression. In the present study, more than 50% of type IIa+IIc and 70% of type IIc+IIa tumors were submucosal carcinomas of less than 20 mm; type IIa showed no significant difference in the rate of submucosal invasion compared to the polypoid type. Not all superficial types are at risk of submucosal invasion. Central depression is an important macroscopic (and endoscopic) sign in regard to their invasiveness.

Earlier studies suggested that the nonpolypoid growth pattern may be a risk factor for lymph node metastasis of submucosal colorectal carcinomas [3, 7, 9]. However, in our series, none of the superficial subtypes had a significantly higher incidence of lymph node metastasis than the polypoid lesions. Lymph node metastasis was found in 6% to 10% (average 8%) of superficial subtypes, similar to a mean value (8.5%) calculated from a nationwide questionnaire that included 19 institutions in Japan [24]. In addition to histologic differentiation and lymphatic permeation, which have been generally accepted as risk factors for lymph node metastasis of colorectal carcinoma [25–27], the depth of cancer invasion in the submucosa is now regarded as an important risk factor [28, 29]. Stratifying the amount (depth and horizontal spread) of submucosal invasion by the carcinoma, no differences in the incidence of lymph nodal metastasis were seen among our superficial subtypes and polypoid type cancer (unpublished data). The findings of the earlier studies may be explained by a lack of considering the amount of cancer invasion to the submucosa. A gross appearance indicating a superficial type may not by itself imply aggressive tumor behavior.

Generally in Japan, superficial-type colorectal cancers are thought to arise de novo, as most earlier studies indicated that their rate of an accompanying adenomatous component was low (0–20%) [1, 3, 6–8]. These studies cannot be accepted outright, though, as it was not shown that they were confined to intramucosal carcinoma. If submucosal carcinomas without a residual intramucosal component (a phenomenon wherein the intramucosal component was destroyed and sloughed away as the carcinoma invaded deep into the submucosa) are examined, they are inevitably seen not to have residual adenoma (as there is no mucosal remnant); hence, by definition, all of them would be recorded as having a de novo origin. Obviously, this is not logical. Furthermore, failure to identify a residual adenomatous component does not indicate that the carcinoma arises de novo, as the carcinoma may have replaced a preexisting precursor adenoma [30, 31].

In our study, the rate of residual adenoma of superficial-type intramucosal carcinoma was significantly lower than its polypoid counterpart (56% vs. 85%). Apparently, the superficial type consists of two groups with different histogenetic pathways. Among types IIa and IIa+IIc, 64% and 52%, respectively, had accompanying adenoma. They thus would have developed from a small flat adenoma [32, 33] through the adenoma–carcinoma sequence and were smaller than those of polypoid type. In contrast, type IIc+IIa (and type IIc), which had no adenomatous component, may have originated via de novo cancerization or the adenoma–carcinoma sequence and were of minute size compared to types IIa and IIa+IIc.

Superficial-type lesions are believed to play an important role in the development of colorectal carcinoma: At least 71.2% [7] to 80.0% [11] of advanced colorectal carcinomas are thought to have arisen from a superficial-type intramucosal carcinoma. Whether

Table 1. Histopathologic characteristics of early colorectal carcinoma by macroscopic type.

Parameter	Polypoid type (type I)	Nonpolypoid (superficial) type (type II)			
		Total	IIa	IIa+IIc	IIc+IIa
Incidence					
Ca-m (n = 643)	503 (78%)	140 (22%)	100 (16%)	27 (4%)	13 (2%)
Ca-sm (n = 414)	302 (73%)	112 (27%)	47 (11%)	40 (10%)	25 (6%)
Average size (mm)*					
Ca-m	21.9 ± 17.6	12.6 ± 7.0	12.2 ± 7.9	13.8 ± 8.0	14.0 ± 6.0
Ca-sm	24.6 ± 13.5	14.2 ± 6.6	13.5 ± 6.1	14.0 ± 5.3	14.5 ± 7.3
Histologic grade					
Well differentiated	756 (93.9%)	234 (92.9%)	134 (91.2%)	64 (95.5%)	36 (94.7%)
Moderately differentiated	46 (5.7%)	14 (5.6%)	11 (7.5%)	1 (1.5%)	2 (5.3%)
Poorly differentiated	3 (0.4%)	4 (1.5%)	2 (1.3%)	2 (3.0%)	0
Rate of sm invasion					
Total**	302/805 (38%)	112/252 (44%)	47/147 (32%)	40/67 (60%)	25/38 (66%)
≤5 mm***	1/26 (4%)	7/28 (25%)	4/23 (17%)	2/4 (50%)	1/1 (100%)
<10 mm****	13/114 (11%)	23/77 (30%)	13/53 (25%)	6/7 (35%)	4/7 (57%)
<20 mm†	117/401 (29%)	90/204 (44%)	38/122 (31%)	32/54 (59%)	20/28 (71%)
Rate of residual adenoma‡	425/503 (85%)	78/140 (56%)	64/100 (64%)	14/27 (52%)	0/13 (0%)
Lymph node metastasis	18/166 (11%)	4/48 (8%)	2/20 (10%)	1/16 (6%)	1/15 (7%)

Ca-m: intramucosal carcinoma; Ca-sm: submucosal carcinoma; sm: submucosa.
*I vs. II: $p < 0.001$.
**I vs. II; $p = 0.058$; I vs. IIa, NS; I vs. IIa+IIc, IIc+IIa, $p < 0.001$.
***I vs. II, $p < 0.01$; I vs. IIa; NS; I vs. IIa+IIc, IIc+IIa, $p < 0.05$.
****I vs. II, $p < 0.01$; I vs. IIa, NS; I vs. IIa+IIc, IIc+IIa, $p < 0.05$.
†I vs. II, $p < 0.01$; I vs. IIa, NS; I vs. IIa+IIc, IIc+IIa, $p < 0.001$.
‡I vs. II; $p < 0.001$; IIa, IIa+IIc vs. IIc+IIa, $p < 0.001$.

superficial-type intramucosal carcinoma is a major precursor of advanced colorectal carcinoma is of more than academic interest. If it is so, clinical investigations must focus on such lesions to avoid the development of advanced carcinoma.

The role of superficial-type intramucosal carcinoma as a precursor of advanced cancer can be estimated by assessing the proportion of submucosal carcinomas that have originated from superficial intramucosal carcinoma by direct histopathologic evaluation [34]. Assessing the proportion of lesions among the intramucosal carcinomas is superficial, however, because it is not certain that all intramucosal carcinomas progress to advanced carcinoma within the life-span of the host. In our series, the polypoid type accounted for 78% of the intramucosal carcinomas, which does not mean that 78% of advanced cancers originated from polypoid-type intramucosal carcinomas. In a previous study [34] we investigated the thickness of the remnant intramucosal component of 106 submucosal carcinomas. Of these 106 lesions, 45 (42%) were judged to originate from superficial-type intramucosal carcinoma because the thickness of the remnant mucosa was less than twice the thickness of surrounding normal mucosa, which corresponds to our definition of the superficial type lesion [18]. Of 45 lesions, 10 (9%) were thought to originate from the superficial depressed (type IIc+IIa or IIc) type lesion. The discrepancy that only 27% of submucosal carcinomas were the superficial type is explained by the fact that a certain proportion of superficial-type intramucosal carcinomas transform their gross configuration to the polypoid type in accordance with their massive invasion of the submucosa. Although not as frequently as in earlier studies [7, 11], it is suggested that at least 42% of advanced colorectal cancers originate from superficial-type intramucosal carcinomas, which can easily be overlooked by many colonoscopists [22].

Résumé

L'incidence et les caractéristiques histopathologiques du cancer colorectal non-polypoïde au début (cancer superficiel) ont été étudiés et comparés aux cancers du type polypoïde. Le type superficiel a été divisé en plusieurs sous-groupes: élevé (type IIa), type IIa avec dépression centrale (type IIa+IIc), ordinaire (type IIb), déprimé (type IIc) et type IIc avec élévation marginale (type IIc+IIa). Le type superficiel représente, respectivement, 22% et 27% des cancers intramuqueux et sous-muqueux. On n' a jamais retrouvé un type IIb pure et il y avait seulement trois cas de type IIC pure. L'envahissement de la sous-muqueuse a été significativement plus fréquent dans les types IIa+IIc et IIc+IIa (et IIc) en cas de petite taille (59% et 71% lorsque la taille de la tumeur était de moins de 20mm) comparé au type polypoïde alors qu'il y avait aucune différence dans le type IIa. Il n'y avait aucune différence significative dans l'incidence de métastase ganglionnaire des cancers de la sous-muqueuse entre les types superficiel et polypoïde. 64% et 52% des cancers du type IIa et IIa+IIc étaient accompagnés d'adénome résiduel, suggérant que ces cancers ont pris naissance à partir d'adénomes plat plus petits dans la séquence adénome-cancer alors qu'il n'y avait aucun élément adénomateux dans les cancers du type IIc+IIa (et IIc) impliquant une cancérisation *de novo* ou un cancer prenant naissance dans une séquence adénome-cancer de plus petite taille comparés aux types IIa et IIa+IIc. Le cancer colorectal au début du type superficiel n'est pas rare. Sa nature n'est pas univoque. Le type superficiel avec dépression centrale est caractérisé par un envahissement rapide de la sous-muqueuse alors que les types IIc+IIa et IIc pourraient prendre naissance *de novo*. En dépit de leur tendance à l'envahissement rapide de la sous-muqueuse, on

ne peut affirmer que ces tumeurs soient plus agressives que les tumeurs polypoïdes.

Resumen

Se efectúa un estudio comparativo sobre la frecuencia y características histológicas de los cánceres colorrectales precoces, tanto polipoideos como no-polipoideos (tipo superficial). El estadio superficial fue subclasificado en: cáncer elevado (tipo IIa), tipo IIa con depresión central (tipo IIa + IIc), cáncer plano (tipo IIb), deprimido (tipo IIc) y tipo IIc con elevación de los márgenes tumorales (tipo IIc + IIa). Dentro del cáncer superficial registramos un 22% de cánceres intramucosos y un 27% con invasión submucosa. No constatamos ninguna tumoración del tipo IIb y sólo tres del tipo IIc. Los cánceres pequeños de los tipos IIa + IIc y IIc + IIa (y IIc) mostraron una alta tasa de invasión submucosa (59% y 71%, para tamaños menores de 20 mm). Comparándose estos hechos con los cánceres del tipo IIa, no se encontraron diferencias significativas. La frecuencia de metástasis ganglionares en neoplasias submucosas fue semejante entre los cánceres superficiales y los polipoideos. En el 64% de los cánceres tipo IIa y en el 52% de los IIa + IIc se encontraron restos de tejido adenomatoso, hallazgo que indica que pueden originarse de un pequeño adenoma plano a través de la secuencia adenoma-carcinoma. En las neoplasias de los tipos IIc + IIa (y IIc) no existe componente adenomatoso alguno, lo que sugiere más que una transformación según la secuencia adenoma-carcinoma, una cancerogénesis "de novo", hipótesis que se afianza al estudiar comparativamente los tipos IIa y IIa + IIc. El cáncer colorrectal superficial precoz no es infrecuente, pero carece de un patrón histológico único. El rápido crecimiento invasivo submucoso es típico de los cánceres superficiales deprimidos centralmente (en escudilla). Sólo los cánceres deprimidos (tipo IIc + IIa y IIc) tienen un posible origen "de novo". Dado el tiempo, que en su rápido crecimiento tardan en invadir la submucosa, no puede afirmarse que sean más agresivos que los cánceres de tipo polipoideo. Histopathologic characteristics of early colorectal carcinoma by macroscopic type.

Acknowledgments

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