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Serrated and Microtubular Colorectal Adenomas in Italian Patients. A 5-year Survey

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Abstract. *Colorectal adenomas from 1552 Italian patients were histologically classified into tubular (TAs), tubulo-villous (TVAs), villous (VAs), serrated (SAs) and microtubular (MTAs). The purpose was to compare the results to those in 3135 colorectal adenomas from Swedish patients. Of the 1552 adenomas, 827 (53%) were TAs, 352 (23%) TVAs, 196 (12%) VAs, 102 (7%), SAs and 14 (0.9%) MTAs. The remaining 61 (4%) were of combined phenotypes (COMBAs). The percentage of VA (considered as the most important dysplastic precursor of colorectal cancer) was higher in Florence than in Stockholm. Notably, the incidence of colorectal cancer in males was also higher in Florence ($78.6/10^5$) than in Stockholm ($57.2/10^5$). Notwithstanding, the highest rate of submucosal invasion (7%) was found among SAs. The diameter of the largest section was used to define the size of the largest adenoma in individual patients. Of the 1380 neoplasias measuring ≤12 mm, only 0.9% (n=13) had invasive carcinomas, but as many as 8.1% (n=14) of the 172 neoplasias measuring ≥13 mm. SAs and MTAs are special adenoma phenotypes with particular morphological and cell proliferative attributes at variance from those of TAs, VAs or TVAs. In the light of the present results, it is proposed that SAs and MTAs are included in future reports of colorectal adenomas in order to compare their frequency worldwide.*

Colorectal adenomas are usually classified on the basis of their histological configuration into 3 structural categories: tubular, tubulo-villous and villous (1). In a large a series of colorectal adenomas (>1000 cases in Table I) Muto, Bussey and Morson (2) found that of 2506 adenomas, 75% were tubular, 15% tubulo-villous and the remaining 10% were villous adenomas. In another large survey, the National Polyp Study Group (3) found that of 3358 colorectal adenomas, 87% were tubular, 8% tubulo-villous and the remaining 5% villous adenomas, and subsequently the Arizona Cancer Center (4) found, in 1218 adenomas, that 65% were tubular, 25% tubulo-villous, and 5% villous; the remaining 5% were classified as unspecified or incipient. In another study, The Italian Multicentre Study Group (5) found, in 1693 adenomas, that 67% were tubular, 27% were tubulo-villous and the remaining 6% were villous adenomas.

A few years ago Longacre and Fenoglio (6) described a fourth phenotype, namely the serrated adenoma, characterized by villous-like fronds with scalloped borders. More recently, we (7) reported a fifth histological phenotype built with villous-like fronds furnished with microtubular structures arranged in a sequential fashion along the slopes of the fronds. That adenoma was initially referred to as villomicroglandular adenoma and more recently as microtubular adenoma by the WHO (8). However, despite the fact that five different histological phenotypes of colorectal adenomas are now on record, colorectal adenomas continue to be classified into three histological categories (2-5).

In a previous study (9), we investigated 3135 colorectal adenomas in Swedish patients. The adenomas were histologically classified into the five aforementioned subtypes. The results showed that 66% were tubular, 18% tubulo-villous, 9% villous, 6% serrated and the remaining 1% were microtubular adenomas.

The purpose of the present work was two fold: i) to assess the frequency of tubular, tubulo-villous, villous, serrated and microtubular colorectal adenomas collected at this Department of Pathology during a period of five years, and ii) to compare the results with those previously reported in Swedish patients (9), as well as in other large series of cases (2-5).

Materials and Methods

The material comprised 1552 patients having one or more colorectal adenomas diagnosed during the previous 5 years (January 1995-December 1999) at the Department of Pathology and Oncology, University of Florence, Italy. Excluded from these

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Table I. *The histological classification of colorectal adenomas reported in larger series.*

Adenoma phenotype	St Mark's Hospital (n=2506)	Polyp Study Group (n=3358)	Arizona Cancer Center (n=1218*)	Italian Multicenter Study Group (n=1693)	Stockhom (n=3135)	Present series (n=1552)	All series (n=13462)
TA	1880 (75)	2920 (87)	842 (69)	1132 (67)	2074 (66)	827 (53)	9675 (72)
TVA	376 (15)	270 (8)	317 (26)	460 (27)	551 (18)	352 (23)	2326 (17)
VA	250 (10)	168 (5)	59 (5)	101 (6)	281 (9)	196 (13)	1055 (8)
SA					202 (6)	102 (7)	304 (6.5)**
MTA					27 (0.8)	14 (0.9)	41 (0.9)**
COMBA						61 (4)	61 (4)

* 69 additional adenomas were unspecified

** Results for Stockhom and the present series only, comprising 4687 adenomas.

TA (tubular adenoma), TVA (tubulo-villous adenoma), VA (villous adenoma),
SA (serrated adenoma), MTA (microtubular adenoma), and COMBA (combined phenotypes phenotypes other than TVA).

series were patients who had familial adenomatous polyposis (FAP), nonpolyposis colorectal cancer (HNPCC), or inflammatory bowel disease (IBD). All adenomas were removed by polypectomy under endoscopic control. Filed hematoxylin and eosin (H&E)-stained sections were reviewed.

Definitions (9). Following the WHO (8), the adenomas were defined by the presence of intraepithelial neoplasia, histologically characterized by hypercellularity with enlarged hyperchromatic nuclei, varying degrees of cellular stratification and loss of polarity. The nuclei may be spindle-shaped, or enlarged and ovoid. Dysplasia in adenomas was subclassified into low-grade dysplasia (LGD) and high-grade dysplasia (HGD) (8). Following the criteria proposed by Fenoglio-Preiser (10), LGD was regarded as a lesion built of dysplastic nuclei "confined to the basal halves of the cells", and HGD as a lesion with "nuclear stratification that extends beyond the midportion of the cells" in three or more glands. To assess HGD, high-power examination was often required.

Tubular adenoma (TA): An adenoma having at least 80% of the dysplastic glands arranged as tubules.

Villous adenoma (VA): An adenoma having at least 80% of the dysplastic glands arranged as straight villous fronds. Villous architecture was considered when the length of the glands exceeded twice the thickness of the normal colorectal crypts.

Tubulo-villous adenoma (TVA): An adenoma exhibiting both tubular and villous adenomatous glands not surpassing the upper limits for TA or VA. For many years this mixed adenoma phenotype has been regarded as a separate type of adenoma, both in diagnostic work and in small and large surveys. Consequently, TVAs are considered as a separate group in the present work.

Serrated adenoma (SA): An adenoma exhibiting, in more than 50%, elongated dysplastic crypts with crenate, sawtooth-like structural changes due to scalloped epithelial infolding. The remaining adenomatous tissue usually showed villous structures. Initially, only the cells at the lower part of the crypts were found to be dysplastic, but in larger adenomas the dysplastic epithelium was also present in the upper part of the crypts.

Microtubular adenoma (MTA): An adenoma having, in more than 50%, fronds exhibiting garlands with consecutive microtubuli located lengthwise along the fronds. The remaining adenomatous tissue usually showed either villous and /or serrated structures.

Combined adenoma (COMBA): An adenoma having simultaneously two or more different histological phenotypes (other than TVAs).

Invasive carcinoma in adenomas: Adenomas in which the neoplastic cells had penetrated through the *muscularis mucosa* into the submucosa (8) (or beyond). In patients having two or more adenomas, the adenoma with the highest degree of intraepithelial neoplasia was selected to classify cases. In patients having two or more adenomas with the same degree of intraepithelial neoplasia, the case was arbitrarily classified either as VA, SA, MTA, TVA, TA or COMBA (in that order) when one of the adenomas displayed one of those phenotypes.

The size of the adenoma was not always available in clinical or pathological reports. Therefore, the diameter of the largest section, measured with a ruler, was used to define the size of the largest adenoma in individual patients with one or more adenomas. Adenomas were subdivided into those measuring ≤ 6mm, 7-8 mm, 9-10 mm, 11-12 mm, 13-14 mm, 15-16 mm, 17-18 mm, 19-20 mm or >20 mm. Blind pilot measurements in 20 unselected cases indicated that the method was reproducible.

Table II. *The histological phenotype in 1552 colorectal neoplasias in Italian patients. Percent in brackets.*

Histological phenotype	LGD	HGD	Submucosal	Total carcinoma
TA	435 (52.6)	387 (46.8)	5 (0.6)	827 (100)
TVA	82 (23.3)	268 (76.1)	2 (0.5)	352 (100)
VA	41 (20.9)	146 (74.5)	9 (4.6)	196 (100)
SA	19 (18.6)	76 (74.5)	7 (6.9)	102 (100)
MTA	9 (64.3)	4 (28.6)	1 (0.7)	14 (100)
COMBA	5 (8.2)	53 (86.7)	3 (4.9)	61 (100)
Total	591 (38.1)	934 (60.2)	27 (1.7)	1552 (100)

LGD: Low-grade dysplasia, HGD: High-grade dysplasia.
TA (tubular adenoma), TVA (tubulo-villous adenoma), VA (villous adenoma), SA (serrated adenoma), MTA (microtubular adenoma), and COMBA (combined phenotypes other than TVA).

Table III. *The histological phenotype in 457 colorectal neoplasias in younger patients (≤59 years of age). Percent in brackets.*

Histological phenotype	LGD	HGD	Submucosal	Total carcinoma
TA	162 (58.5)	114 (41.1)	1 (0.3)	277 (100)
TVA	20 (22.2)	70 (77.8)	0 (0)	90 (100)
VA	9 (19.1)	35 (74.4)	3 (6.3)	47 ()
SA	4 (16.7)	18 (75.0)	2 (8.3)	24 (100)
MTA	3 (75.0)	1 (25.0)	0 (0)	4 (100)
COMBA	2 (13.3)	12 (80.0)	1 (6.7)	15 (100)
Total	200 (43.8)	250 (54.7)	7 (1.5)	457 (100)

LGD: Low-grade dysplasia, HGD: High-grade dysplasia.
TA (tubular adenoma), TVA (tubulo-villous adenoma), VA (villous adenoma), SA (serrated adenoma), MTA (microtubular adenoma), and COMBA (combined phenotypes other than TVA).

Table IV. *The histological phenotype in 1095 colorectal neoplasias in elderly patients (≥60 years of age). Percent in brackets.*

Histological phenotype	LGD	HGD	Submucosal carcinoma	Total
TA	273 (49.6)	273 (49.6)	4 (0.7)	550 (100)
TVA	62 (23.7)	198 (75.5)	2 (0.8)	262 (100)
VA	32 (21.5)	111 (74.4)	6 (4.0)	149 (100)
SA	15 (19.2)	58 (74.3)	5 (6.4)	78 (100)
MTA	6 (60.0)	3 (30.0)	1 (10.0)	10 (100)
COMBA	3 (6.5)	41 (89.1)	2 (4.3)	46 (100)
Total	391 (35.7)	684 (62.4)	20 (1.8)	1095 (100)

LGD: Low-grade dysplasia, HGD: High-grade dysplasia.
TA (tubular adenoma), TVA (tubulo-villous adenoma), VA (villous adenoma), SA (serrated adenoma), MTA (microtubular adenoma), and COMBA (combined phenotypes other than TVA).

Table V. *The histological phenotype in 967 colorectal neoplasias in male patients. Percent in brackets.*

Histological phenotype	LGD	HGD	Submucosal carcinoma	Total
TA	290 (56.3)	222 (43.1)	3 (0.6)	515 (100)
TVA	52 (25.5)	151 (74.0)	1 (0.4)	204 (100)
VA	31 (23.7)	95 (72.5)	5 (3.8)	131 (100)
SA	11 (16.9)	50 (76.9)	4 (6.2)	65 (100)
MTA	4 (57.1)	2 (28.6)	1 (14.3)	7 (100)
COMBA	3 (8.3)	31 (86.1)	2 (5.6)	36 (100)
Total	391 (40.8)	551 (57.5)	16 (1.7)	958 (100)

LGD: Low-grade dysplasia, HGD: High-grade dysplasia.
TA (tubular adenoma), TVA (tubulo-villous adenoma), VA (villous adenoma), SA (serrated adenoma), MTA (microtubular adenoma), and COMBA (combined phenotypes other than TVA).

Table VI. *The number of adenomas/patient (ratio in brackets) in 1925 colorectal neoplasias. Percent in brackets.*

Histological phenotype	LGD	HGD	Submucosal carcinoma	Total
TA	507/435 (1.2)	476/387 (1.2)	9/5 (1.8)	992/827 (1.2)
TVA	91/82 (1.1)	332/268 (1.2)	4/2 (2.0)	427/352 (1.2)
VA	50/41 (1.2)	199/146 (1.4)	13/9 (1.4)	262/196 (1.3)
SA	23/19 (1.2)	98/76 (1.3)	11/7 (1.6)	132/102 (1.3)
MTA	15/9 (1.7)	7/4 (1.7)	2/1 (2.0)	24/14 (1.7)
COMBA	6/5 (1.2)	74/53 (1.4)	8/3 (2.7)	88/61 (1.4)
Total	692/591 (1.2)	1186/934 (1.3)	47/27 (1.7)	1925/1552 (1.2)

LGD: Low-grade dysplasia, HGD: High-grade dysplasia.
TA (tubular adenoma), TVA (tubulo-villous adenoma), VA (villous adenoma), SA (serrated adenoma), MTA (microtubular adenoma), and COMBA (combined phenotypes other than TVA).

Table VII. *The size (in mm) in 27 colorectal neoplasias with submucosal invasion.*

Histological phenotype	≤ 12mm (n=1380)	≥13 mm (n=172)	Total n=1552
TA	3	1	4
TVA	1	-	1
VA	4	5	9
SA	2	5	7
MTA	1	2	3
COMBA	2	1	3
Total	13	14	27

The entire collected material was reviewed twice by one of us (CR). The second review was done without knowledge of the first evaluation. The results presented in Tables I-VII are based on the results of the second evaluation. The results obtained in the second evaluation were subsequently compared to the original reports at this hospital. This was done to study possible interobserver variation.

Sections from 28 selected adenomas (seven TAs, seven VAs, seven SAs, and seven MTAs) were stained with anti-human Ki67 antigen (clone MIB1, DAKO Cytomation, Glostrup, Denmark).

Statistical analysis. The non-parametric test of Wilcoxon was done using StatView Version 4.5 software (Abacus Concepts, Berkley, CA, USA). Statistical significance was defined as $p<0.05$.

Results

Patient characteristics. Colorectal adenomas were investigated in 1552 patients. Of the 1552 patients, 1093 (71 %) occurred in elderly patients (*i.e.* 60 years of age or older). The remaining 459 (29%) occurred in younger patients (*i.e.* 59 years of age or younger). Of the 1552 patients, 967 (62%) were males and the remaining 585 (38%) females.

Histological phenotypes. Table I shows that, of the 1552 patients, 827 (53%) were TAs, 352 (23%) TVAs, 196 (12%) VAs, 102 (7%) SAs, 14 (0.9%) MTAs and the remaining 61 (4%) were COMBAs. Table II shows that 591 or 38% of the 1552 neoplasias had low-grade dysplasia (LGD), 934 (60%) high-grade dysplasia (HGD) and 27 (2%) showed submucosal invasive carcinoma.

Table II also shows that the highest percent of adenomas with HGD (87%) was recorded among COMBAs and the lowest (29%) among MTAs. The percent of COMBAs with HGD was significantly higher than for MTAs or TAs with HGD ($p<0.05$).

Adenomas with invasive adenocarcinoma. The highest rate of adenomas with invasive adenocarcinoma was recorded in SAs (7%). The percent of SAs with invasive adenocarcinoma was significantly higher than in TAs or TVAs with invasive adenocarcinoma ($p<0.05$).

Age and histological phenotypes. The results obtained in younger (≤ 59 years of age) and in elderly patients (≥ 60 years of age) are shown in Tables III and IV, respectively. Of the 1552 colorectal neoplasias, 457 (29%) occurred in younger patients (Table III) and the remaining 1095 (71%) among elderly patients (Table IV). The percent of colorectal neoplasias in elderly patients was significantly higher than in younger patients ($p<0.05$). As a comparison, 63% of 3135 colorectal neoplasias in the Swedish material (9) occurred in elderly patients. Thus, in spite of the fact that in the present material the proportion of elderly patients was somewhat higher than in the Swedish survey (9), no essential differences in age were found between the two series. From Tables III and IV, it may be deduced that the proportion of adenomas with HGD were somewhat higher among elderly patients (62%) than among younger patients (55%), but the difference was not significant ($p=0.6$).

Gender and histological phenotypes. Table V shows that 958 (62%) of the 1552 neoplasias occurred in male patients. The difference between the proportions of male and female patients (data in females not shown) having neoplasias with LGD, HGD, or submucosal carcinoma was not significant ($p=0.6$).

Number of adenomas/patient. A total of 1925 adenomas were found in the 1552 patients investigated (Table VI) or 1.2 adenomas/patient. Of the 1925 adenomas, 66.8% (n=1287) were solitary and the remaining 33.2% (n=638) multiple (2.6 adenomas /patient, range 2-5). For comparison, of the 3135 colorectal adenomas in Swedish patients(9), 60% (n=1892) were solitary and the remaining 40% (n=1243) were multiple (2.2 adenomas /patient in 549 patients). Thus, no essential difference was found between the number of adenomas/patient in the two surveys.

The number of adenomas without invasion/patient was similar in those having LGD (1.2 adenomas/patient) and those having HGD (1.3 adenomas/patient). Although the number of adenomas/patient was somewhat higher in patients having adenomas with invasive adenocarcinoma (2.0 adenomas/patient), the difference was non-significant ($p=0.6$).

Size in adenomas and submucosal invasion. The results in Table VII indicate that, of the 1380 neoplasias measuring ≤12 mm, only 13 or 0.9% had invasive adenocarcinoma. On the other hand, of the 172 neoplasias measuring ≥13 mm, 14 or 8.1% had invasive adenocarcinoma. The difference was significant ($p<0.05$).

Discussion

Only a few studies (2-5) have been done to assess the histological characteristics of colorectal adenomas in a relatively large number of lesions comprising more than 1000 adenomas. In those reports, adenomas were classified into 3 subtypes: tubular, tubulo-villous and villous. Fenoglio-Preisser (10) classified colorectal adenomas into four categories: tubular, tubulo-villous, villous and flat or depressed lesions.

More recently, colorectal adenomas were classified into 5 histological subtypes (9, 11): TAs, TVAs, VAs, SAs and MTAs. A similar histological classification was applied in this study to 1925 colorectal adenomas found in Italian patients. This material included an additional group amalgamating 2 or more histological phenotypes (other than TVAs); it was termed COMBA (*i.e.* combined adenoma). The results indicated that 53% of the adenomas were TAs, a percentage that was lower than the percent of TAs reported in Swedish (66%) (9) as well as in patients from other series (*cf.* Table I). In the present material, TVAs accounted for 23% of the adenomas, a percentage that was higher than for Swedish patients (18%) (9), but similar to those found in a previous study in Italian (5) and American (3) patients (*cf.*Table I). VAs accounted for 13% of the adenomas in the present survey, a somewhat higher percentage than the one recorded in Stockholm (9%) (9) as well as in patients from other series (Table I), but much lower than in Fenoglio-Preiser's experience (10) in which "approximately 20% of asymptomatic persons screened by colonoscopy have villous adenomas". It should be mentioned that VA is considered to be the single most important dysplastic precursor of sporadic colorectal cancer (2). Considering that the crude rate annual incidence of colorectal cancer in Florence is $78.6/10^5$ for males and $71.9/10^5$ for females, but only $57.2/10^5$ for males and $56.3/10^5$ for females in Stockholm, it is conceivable that the higher percent of VAs in this series has some bearing on the higher incidence of colorectal cancer in this city (as compared to that in Stockholm).

SAs accounted for 7% of the adenomas and MTAs for 0.9%. Similar percentages of SAs and MTAs (namely 6% and 1%, respectively) were reported in Swedish patients (9). Recently, Bariol *et al.* (12) found, among 255 colorectal polyps, that 3.5% were serrated adenomas and 1.5% "admixed" polyps (having hyperplastic and serrated adenomatous components). Thus, the total percent of serrated adenomas with or without hyperplastic components in Bariol *et al.'s* (12) series should be 5%, a percentage similar to the one reported here (7%) and identical to that reported in a previous study (5%) (9). It is conceivable that, in the other series (2-5), SAs, MTAs and COMBAs were included among VAs or TVAs.

SAs and MTAs are special adenoma phenotypes with particular structural and cell proliferative attributes that differ from those of TAs, VAs or TVAs (9, 11). The present studies with Ki67 (clone MIB1) in 28 selected adenomas confirmed previous studies (13, 14), indicating that cell proliferation in TAs and VAs occurs initially in the upper part of the dysplastic glands. In contrast, cell proliferation in SAs is initially found in the lower part of the crypts (13, 14), whereas in MTAs it occurs in the deeper part of individual "rings" (11). Because of those distinctive morphological features and cell proliferation characteristics, SAs and MTAs are now regarded as independent adenoma phenotypes, at variance with TAs, TVAs and VAs. The recognition of SAs seems important considering that, in this series, SAs were associated with a relatively high frequency of submucosal invasion (7%). This finding is remarkable considering that Jass (15) recently calculated that up to 6% of invasive colorectal carcinomas could originate from serrated adenomas.

Yashiro *et al.* (16) demonstrated that serrated adenomas of the colon have a unique pattern of genetic alterations

that distinguishes them from other colorectal polyps, as they often show loss of heterozygosity (LOH) on 18 q., suggesting that serrated adenomas may be generated through a genetic pathway that differs from that in other colorectal adenomas. It is conceivable that the molecular stimuli (17, 18) that trigger the development of foci of dysplastic mucosal proliferation – known as colorectal adenomas – may be at variance with the molecular events that generate the "etching" of tubular, tubulo-villous, villous, serrated or microtubular configurations (11).

In the first evaluation, 12 adenomas recorded as having tightly packed, confluent, possibly microtubular formations, were ascribed in the second evaluation to the TA (n=4) and TVA (n=2) subgroups. The opinion that SAs, MTAs and COMBAs had probably been classified as VAs or TVAs in other series (Table I) seems to be substantiated by the fact that no case of SA, MTA and COMBA appeared in the original pathological reports from this hospital. That fact precluded a study of possible interobserver variations in this material. It should be pointed out that the significance of interobserver studies has recently been questioned. Several interobserver trials (19-22) do not present an acceptable level of reproducibility. Because of these limitations, we refrained from studying the magnitude of the interobserver variation among the authors in this survey.

Several studies have shown that the presence of an invasive adenocarcinoma in an adenoma is greatly influenced by the size of the adenomas. In a classical report, Muto *et al.* (2) found that submucosal invasion was present in 1.0% of the TA adenomas measuring <1 cm and in 9.5% of the VAs, whereas in those >2 cm, invasion had occurred in 34.7% of the TAs and in 52.9% of the VAs. In that important survey (2) it was stated that the size of the lesions "was assessed from examinations of clinical records (including surgical operation notes) and pathology department reports. In some cases this could be measured from the histological sections". It is apparent that, in that classical work, the size of the adenomas was assessed by three different methods. The number of cases in which there was a discrepancy between the size in clinical records (including surgical operation notes) and in pathology records was not specified. In addition, more recent studies have shown that the "eye ball" method of measuring colonic polyps at endoscopy is not accurate; an interobserver study of estimates of polyp size by eight experienced endoscopists was unacceptably low, namely 35% (23).

Since in the present work the size of the adenomas was not always available in clinical or pathological reports, we opted for measuring the largest diameter of the largest section in all cases as a way to define the size of the largest adenoma in individuals having one or more adenomas. Our measurements indicated that an invasive adenocarcinoma was present in only 0.9% of the adenomas measuring ≤12 mm, but in as many as in 8.1% of the adenomas measuring ≥13 mm. Bearing in mind that the "eye ball" technique to calculate adenoma size is inaccurate (23), the method used in this communication seems to offer an alternative approach to assess the size of colorectal adenomas. That simple method may prove of value in standardizing measurements of colorectal adenomas in large series of cases (>1000 adenomas) at hospitals from disparate geographical regions.

In the light of the present and previous (9, 11) results, it is suggested that SAs (and MTAs) are included in future reports dealing with the histological characteristics of colorectal polyps in order to compare their frequency worldwide.

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