ORIGINAL ARTICLE

Proximal shift of advanced adenomas in the large bowel – does it really exist?

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KEY WORDS

adenoma, advanced adenomatous polyp, colorectal cancer, proximal shift

ABSTRACT

INTRODUCTION During the last decades, the proximal shift in the distribution of colorectal carcinomas (CRCs) has been described. It is uncertain whether the shift is the result of actual changes in CRC incidence or reflects population aging. Most CRCs develop as a result of malignant progression of benign epithelial neoplasms – advanced adenomas (AA).

OBJECTIVES The aim of the study was to investigate whether the proximal shift of AA occurs over time.

PATIENTS AND METHODS Two databases were used. The first one (RETRO) included consecutive patients of the Department of Gastroenterology treated between the years 1981 and 1994. The second one (Colonoscopy Screening Program – CSP) included asymptomatic participants of the colonoscopy screening program recruited between 2000 and 2004 from the Warsaw region. Only patients with AA who underwent total colonoscopy were included in the analysis. AA was defined as adenoma of 10 mm or more in diameter, with high-grade neoplasia, and villous or tubulovillous morphology, or any combination of the above features. The analysis was conducted using 2 different definitions of the proximal segment in the large intestine – either splenic flexure or the bend between the descending and sigmoid colon. To compare the distribution of AA, a multiple logistic regression model was used.

RESULTS AA was located proximally to the splenic flexure in 41 of 200 patients (20.5%) in the RETRO group and 122 of 430 patients (28.4%) in the CSP group. No proximal shift of AA was observed after adjusting for age and sex ($P > 0.1$).

CONCLUSIONS The risk of having proximal AA was similar in both groups. The results suggest the lack of proximal shift in the distribution of advanced colorectal adenomas.

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INTRODUCTION Adenomas of the large bowel are very common in Western populations.[1] These benign epithelial neoplasms, particularly larger polyps with villous architecture and high-grade dysplasia, are frequent precursors of colorectal carcinomas (CRC). Such lesions are commonly described as advanced adenomas (AA).[2] The majority of sporadic CRCs develop from their direct precursors via adenoma-CRC and serrated neoplasia pathways.[3,4] There is a growing interest in CRC prevention, achieved either by endoscopic or pharmacological methods.[5]

During the last decades, several authors suggested an increase in the incidence of proximal colorectal cancers.[6-8] Such a proximal shift and the apparent link between AA and CRC are prerequisites for the expected proximal migration of AA over time. The aim of the study was to test this hypothesis.

PATIENTS AND METHODS Two study cohorts recruited at the Department of Gastroenterology and Hepatology, Medical Center for Postgraduate Education, Warsaw, Poland, were included in the analysis. The first cohort (RETRO) consisted of consecutive symptomatic patients who underwent total colonoscopy with polypectomy of an AA between the years 1981 and 1994. The second cohort

(Colonoscopy Screening Program – CSP) included asymptomatic individuals who underwent total colonoscopy with polypectomy of an AA as part of the National Colorectal Cancer Screening Program between the years 2000 and 2004.[9,10]

Clinical characteristics including age, sex, medical history, endoscopic presence and anatomical localization of each AA as well as its histological type according to the World Health Organization (WHO) 2000 classification were collected.[11] All lesions in the RETRO group were reevaluated and reappraised where necessary to meet the WHO criteria.

Statistical analysis The proportion of patients with at least 1 proximal AA was established as the endpoint of the study. The association between the examination period (RETRO or CSP) and the presence of at least 1 proximal AA was evaluated using a multivariate logistic regression model, including sex and age (25–49, 50–54, 55–59, 60–65 years) as covariates. All tests were 2-sided and the level of significance was set at 5%. All analyses were performed for 2 definitions of proximality.

RESULTS In the RETRO group, the proximal AA was found in 41 of 200 patients (20.5%) according to the first definition of proximality and in 53 of 200 patients (26.5%) according to the second definition of proximality. In the CSP group, the proportions were 122 of 430 patients (28.4%) and 154 of 430 patients (35.8%), respectively. Characteristics of the patients with AA in the RETRO and CSP groups are presented in TABLE 1.

The results of a multivariate analysis of the risk factors for the presence of at least 1 proximal AA are shown in TABLE 2.

We did not observe any differences in the risk of proximal AA between the RETRO and CSP groups, when adjusted for age and sex (P >0.1). Sex was not a statistically significant risk factor for the presence of proximal AA; the differences were at borderline significance (P = 0.059 for the first and P = 0.067 for the second definition of proximality). On the other hand, we showed that the risk of developing at least 1 proximal AA is higher in patients aged from 50 to 54 years compared with younger individuals (for both definitions of proximality).

TABLE 1 Characteristics of patients with advanced adenomas in the study cohorts

		RETRO n = 200	CSP n = 430
sex, male, n (%)		119 (59.5)	209 (48.6)
age	min; max	25; 94	40; 66
	mean ±SD	60.9 ±11.24	56.7 ±5.49

Abbreviations: SD – standard deviation

DISCUSSION During the last decades, a proximal shift in the distribution of colorectal cancer has been postulated. Until 1940, 88% of CRCs were located in the rectum or sigmoid colon.[12] CRCs of the cecum, which used to constitute less than 10% of the cases, now exceed 20%.[13] A significant progress in endoscopic techniques as well as modifications in lifestyle and dietary habits may also contribute to the observed trends. It remains unclear whether it is the biology of CRC that alters or whether the shift is illusory and results from improved diagnostic possibilities and the process of population aging. These controversies have been widely discussed in the literature. Friedenberg et al.[14] analyzed over 11,000 colonoscopies and claimed that the proximal shift of CRC actually exists and cannot be explained otherwise. Ries et al.[15] reported similar findings.Moreover, Cucino et al.[16] showed a 20% increase in the proportion of proximal lesions in white and black populations between the years 1970 and 2000. On the other hand, Rabeneck et al.[17] analyzed 9 population cancer registries with over 200,000 patients and reported that the proximal shift resulted from decreased prevalence of distal CRC and from population aging.

Most data concern the proximal shift of CRC. However, premalignant lesions, particularly AA, have rarely been discussed. In 1987, Gerharz et al.[18] showed, based on autopsy studies, that the incidence of proximal adenomas increases with age. This finding was later confirmed by other investigators.[19,20] Offerhaus et al.[21] described the proximal migration of adenomas (in toto) over 40 years, and in most contemporary Korean papers a significant increase was shown both

TABLE 2 Multivariate analysis of the risk factors for the presence of at least 1 proximal advanced adenoma

		1st definition of proximality			2nd definition of proximality		
		OR	95% CI	P	OR	95% CI	P
sex, male vs. female		1.42	0.99–2.05	0.059	1.37	0.98–1.93	0.067
age, y	25–49			>0.1	1.89	0.94–3.77	0.072
	50–54	2.08	1.02–4.22	0.043	2.13	1.10–4.11	0.024
	55–59			>0.1			>0.1
	60–65			>0.1			>0.1
CSP vs. RETRO				>0.1			>0.1

Abbreviations: CI – confidence interval, OR – odds ratio

in the proportion of patients with proximal adenomas and in "per polyp" analysis during the last 10 years.[22] Additionally, it must be emphasized that various authors use different definitions of proximality. The first approach reflects distinct embryological origin, topography of mesocolon, and 5-fluorouracil chemotherapy responsiveness related to the higher rate of microsatellite instability in the proximal part.[23] In this definition, the splenic flexure constitutes the proximal part of the colon.[24] The second definition of the proximal colon includes also the descending colon, which is in line with the endoscopic perspective illustrating the extent of flexible sigmoidoscopy.[25] To enhance comparability, we performed parallel analyses, in the end reaching similar conclusions.

Our study has several limitations. It seems conceivable that the inclusion of a larger patient group observed more recently could influence the results and possibly confirm the proximal shift postulated by several investigators. It is also arguable whether the comparison between symptomatic and asymptomatic patients is justified. Considering that proximal lesions are usually oligosymptomatic (or even symptomless in the case of adenomas), it is reasonable to assume that in the RETRO group most symptoms were not associated with such lesions. It has to be underlined that due to a negligible effect of adenomas on clinical symptoms, the comparability between RETRO and CSP groups can be rationalized, with all applicable restrictions. The apparent age and sex differences between the groups must be considered in the use of statistical methods. To objectively asses the existence of the proximal shift, a multivariate model was fitted.

In our analysis, the risk of proximal AA in both groups was similar, irrespective of the definition of proximality. Therefore, we support the concept of the illusive nature of proximal shift, as proposed by Rabeneck et al.[17] in reference to CRC. We did not confirm the association between male sex and the incidence of proximal AA (95% confidence interval [CI], 0.99–2.05, P = 0.059, and 0.98–1.93, 0.067, respectively). In the previous studies, men were at a higher risk of developing such lesions.[26] Of note, aging people are expected to have a higher risk of having AA (also in proximal locations). However, we showed only a minor effect, restricted to the age group of 50–54 years (odds ratio [OR], 2.08; 95% CI, 1.02–4.22, P = 0.043 and OR, 2.13; 95% CI, 1.10–4.11, P = 0.024, respectively).

No significant proximal shift of AA was observed. This finding may be particularly valuable in the discussion concerning colorectal cancer and precancerous lesion screening strategies. Endoscopic methods are common, cost-effective, and have been proved to decrease CRC mortality.[27,28] However, the availability of colonoscopy is limited, especially in the developing countries. Flexible sigmoidoscopy, which is safer and better tolerated, allows to visualize only distal 60 cm of the colon. It is widely accepted as a screening tool, considering the predominance of distal lesions.[29,30] If the proximal shift of AA really existed, it could be an additional argument indicating limitation of flexible sigmoidoscopy screening in comparison with full colonoscopy screening. However, as our results show, there is no age-adjusted shift of AA. Thus, our study becomes another voice in an ongoing debate on the optimal screening approach.

In conclusion, there were no significant differences in the risk of developing at least 1 proximal AA between patients in the RETRO and CSP groups after adjusting for age and sex, regardless of the definition of proximality. The results suggest that no proximal shift in the distribution of advanced colorectal adenomas occurs over time.

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ARTYKUŁ ORYGINALNY

Proksymalne przesunięcie występowania zaawansowanych gruczolaków jelita grubego – czy takie zjawisko istnieje?

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gruczolak, proksymalne przesunięcie, rak jelita grubego, zaawansowany polip gruczolakowaty

STRESZCZENIE

WPROWADZENIE W ciągu ostatnich dziesięcioleci opisano proksymalne przesunięcie w dystrybucji raków jelita grubego (RJG). Nie ma pewności, czy przesunięcie wynika z rzeczywistych zmian w zapadalności na RJG, czy odzwierciedla proces starzenia się populacji. Większość RJG rozwija się wskutek złośliwienia łagodnych nowotworów nabłonkowych – zaawansowanych gruczolaków (ZG).

CELE Celem badania było sprawdzenie, czy występuje proksymalne przesunięcie występowania ZG w czasie.

PACJENCI I METODY Wykorzystano dwie bazy danych. Pierwsza (RETRO) obejmowała kolejnych pacjentów Kliniki Gastroenterologii leczonych w latach 1981–1994. Druga (Colonoscopy Screening Program – CSP) obejmowała bezobjawowych uczestników programu kolonoskopowych badań przesiewowych prowadzonych w latach 2000–2004 w rejonie Warszawy. W analizie uwzględniono jedynie pacjentów z ZG, u których przeprowadzono pełną kolonoskopię. ZG definiowano jako gruczolaki o średnicy ≥10 mm, z neoplazją dużego stopnia, o utkaniu kosmkowym lub cewkowo-kosmkowym lub o dowolnym skojarzeniu powyższych cech. Analizy przeprowadzono dla 2 definicji części proksymalnej w jelicie grubym, przyjmując jako granicę zagięcie śledzionowe lub zstępniczo-esicze. W celu porównania rozkładu ZG zastosowano model wieloczynnikowej regresji logitowej.

WYNIKI Obecność ZG położonych proksymalnie do zagięcia śledzionowego stwierdzono u 41 z 200 pacjentów (20,5%) w grupie RETRO oraz 122 z 430 (28,4%) w grupie CSP. Po uwzględnieniu wpływu wieku i płci nie stwierdzono proksymalnej migracji ZG ($p > 0,1$).

WNIOSKI Ryzyko wystąpienia ZG w części proksymalnej było podobne w obu grupach. Wyniki sugerują brak proksymalnego przesunięcia w występowaniu ZG jelita grubego.

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