Influence of mucinous components on survival in colorectal adenocarcinomas: a multivariate analysis

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SUMMARY Of 534 resected colorectal adenocarcinomas, 165 (31%) contained some mucinous components; these represented the main part of the tumour in 67 (13%). Of the mucin containing tumours, 63 (38%) were in the right colon compared with 50 (13%) of the non-mucinous ones (p < 0·001). Patients with predominantly mucinous tumours were significantly older than those with non-mucinous tumours, and they tended to present with tumours at a more advanced stage. A multivariate analysis did not show any significant independent prognostic influence of the mucinous component except when this had a predominantly signet ring cell pattern.

Mucin production is a common histological feature in colorectal carcinomas and when it is abundant such tumours have been regarded as separate histological and clinical entities and have been classified as mucinous, mucoid/colloid adenocarcinomas, or signet ring carcinomas.[1 2] Though patients with such tumours have been considered by many authors to have a poorer prognosis than patients with non-mucinous adenocarcinomas,[3–7] there have been conflicting reports.[1, 8–10] Because of the lack of a precise definition of mucinous adenocarcinomas, especially regarding the quantitative association between mucinous and non-mucinous components, and also because of differences in clinical criteria, the estimation of the true incidence of mucinous carcinomas and comparisons of survival data between patients with mucinous and non-mucinous tumours are difficult.

The aim of this investigation was to study the prognostic importance of mucinous components in colorectal adenocarcinomas. Special attention was paid to the possible prognostic influence of small mucinous areas in otherwise non-mucinous tumours.

Patients and methods

A total of 770 patients with histologically confirmed single carcinomas of the large intestine were treated at the Regional and University Hospital of Trondheim during the years 1964 to 1978.[11] Details of age, sex, site of tumour, size of tumour and clinical stage were abstracted from the clinical and pathological reports. Resections were carried out in 599 patients. The histological slides from the resection specimens were

re-examined by one of us (TBH). To check the reproducibility of the histological evaluation, 212 random cases (35%) were drawn by computer to be seen twice during the review. These cases were sorted in with the others according to a computer generated list.

The histological sections were stained with haemotoxylin and eosin and saffron. In addition, sections with alcian blue were available in most cases. About three sections from each tumour were examined. The deepest infiltrating part of the tumour was represented in at least one of the sections in every case, and in most cases the transitional zone between normal mucosa and the tumour edge was also studied. The rectangular mounted sections measured between about 1 × 1 cm to 1·5 × 3·0 cm.

Only non-mucinous adenocarcinomas, mucinous adenocarcinomas, or signet ring cell carcinomas as defined by the World Health Organisation expert group on histological typing of intestinal tumours,[2] were included in the study.

The tumours were divided into five categories based on a semiquantitative analysis of their mucin content (table 1). Histological grading of the tumours in categories 1 to 4 was by the predominating degree of differentiation present as reported previously for the non-mucinous tumours of this series.[16] The mucinous areas were classified as well differentiated if regular tubules predominated, and as poorly differentiated if highly irregular tubules represented the major component; mucinous tumours of intermediary morphology were graded as moderately differentiated, and signet ring cell carcinomas were not graded (figure). Areas with signet ring cells were found in 17 tumours and predominated in 11 of them.

Table 1 *Tumour categories and histological grades in 534 colorectal carcinomas*

Histological category of tumour	Degree of differentiation			
	Well	Moderate	Poor	Total
Category 1: Mucinous areas absent	121	203	44	369*
Category 2: Non-mucinous areas predominating, and mucinous areas present only in small areas	19	52	16	87
Category 3: Non-mucinous and mucinous areas evenly distributed	1	7	3	11
Category 4: Mucinous areas other than signet ring cell carcinoma predominating	36	17	3	56
Category 5: Signet ring cell carcinoma predominating	0	0	0	11
All categories	177	279	66	534

*One non-mucinous tumour could not be graded.

Ten tumours with areas of undifferentiated carcinoma were excluded from the study, as was one case in which the slides were of bad technical quality. In addition we excluded 43 patients who died of postoperative complications and 11 who were over 85 years of age at the time of admission. There remained 534 tumours from 273 men and 261 women for the study. The mean age (SEM) was 65·4 (0·6) years (range 27 to 85).

The tumours were retrospectively assigned to one of three anatomical sites: the right colon (caecum and ascending colon, n = 113); the left colon (hepatic flexure, transverse colon, splenic flexure, descending, sigmoid and rectosigmoid colon, n = 231), and the rectum (rectum and anal canal, n = 190).

Clinicopathological staging was done retrospectively using Dukes' classification.[12] Tumours with distant metastases or local growth beyond the surgical margins were classified as "advanced disease" (also known as "Dukes' D"). Dukes' A lesions accounted for 13% of the cases, and 65% of these tumours were in the rectum (table 2).

Survival data were obtained from the files of the Cancer Registry of Norway up to the end of September 1986. The causes of death were taken from the death certificates. Death due to colorectal cancer was used as the clinical end point, and patients were studied up to the age of 85.
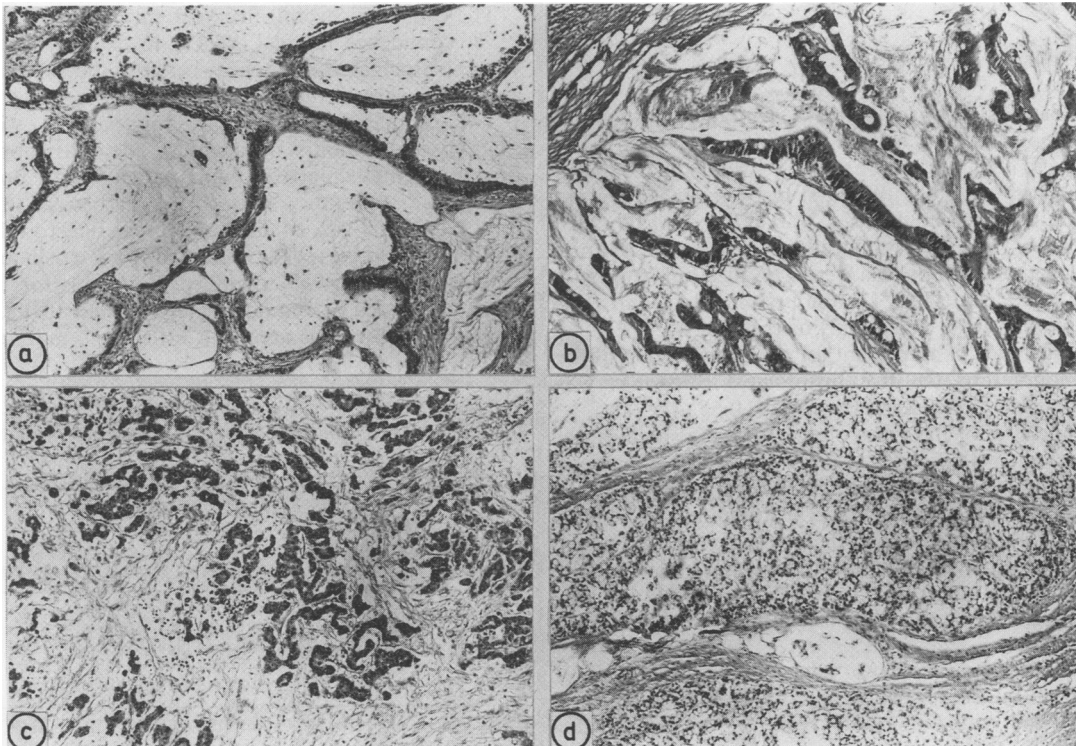

Figure   *Colorectal adenocarcinomas with abundant mucin: (a) well differentiated, (b) moderately differentiated, (c) poorly differentiated, and (d) signet ring cell carcinoma. (Haematoxylin-eosin-saffron.)*

Table 2 Site of tumour and clinicopathological stage in 534 patients operated on for colorectal adenocarcinoma. (Row percentages in parentheses)

Site of tumour	Clinicopathological stage				
	Dukes A	Dukes B	Dukes C	Advanced disease*	All stages
Right colon	7 (6)	52 (46)	38 (34)	16 (14)	113
Left colon	18 (8)	119 (52)	49 (21)	45 (19)	231
Rectum	47 (25)	74 (39)	52 (27)	17 (9)	190
All sites	72 (13)	245 (46)	139 (26)	78 (15)	534

*Denotes disease with distant spread or local tumour growth beyond the surgical margins.

Table 3 Histological categories and sites of tumours in 534 colorectal adenocarcinomas. (Row percentages in parentheses)

Histological category of tumour	Tumour site			All sites
	Right colon	Left colon	Rectum	
1	50 (13)	176 (48)	143 (39)	369
2	26 (30)	31 (36)	30 (34)	87
3	6 (55)	3 (27)	2 (18)	11
4	22 (39)	20 (36)	14 (25)	56
5	9 (82)	1 (9)	1 (9)	11
All tumours	113 (19)	231 (44)	190 (37)	534

Calculations of survivals were based on Kaplan-Meier estimates of the survival curves within the actual patient group using the computer program BMD-PIL.[13] To adjust for stage of tumour, site of tumour, and age and sex of the patient, further statistical analysis was done by the Cox regression model[13 14] with these factors included as covariates in addition to category of tumour and histological grade. Cohen's kappa statistic[15] was used to test the accuracy of the histological classification of the tumours into the five categories.[16]

Results

Of the 534 tumours, 165 (31%) contained a mucinous component (28% in men and 34% in women). The male:female ratios were 0:9 and 1:1 for the mucinous and non-mucinous tumours, respectively. Mucinous areas predominated in 67 (13%) of tumours, of which 11 (2%) were signet ring cell carcinomas. Small areas of mucinous carcinoma were identified in 87 tumours (16%), and in 11 (2%) tumours mucinous and non-mucinous areas were evenly distributed.

The index of agreement for the classification of the tumours into the five histological categories was $\kappa = 0.81$ (95% confidence interval 0.65 to 0.97).

The sites of the types of tumour were significantly different with 63 of 165 (38%) of the mucinous tumours being in the right colon compared with 50 of 369 (13%) of the non-mucinous tumours (p < 0.001) (table 3). More than half the lesions in the right colon contained mucinous components compared with only about a quarter of the left colonic and rectal tumours. Nine of the 11 signet ring cell carcinomas were in the right colon.

The tumours tended to have a poorer prognosis as judged by Dukes' stage as the amount of mucin increased (table 4). Only two of 67 (3%) of the tumours that were predominantly mucinous were Dukes' A lesions, compared with 57 of 369 (16%) and

13 of 98 (13%) for non-mucinous tumours, and tumours with smaller mucinous areas, respectively. None of the 11 signet ring cell carcinomas was a Dukes' A tumour.

The mean age of the patients increased with increasing mucin content of the tumours (table 5) and was significantly higher in patients with predominantly mucinous areas than in patients with non-mucinous tumours (p < 0.01). In patients less than 50 years of age three of 48 (6%) of the tumours were predominantly mucinous adenocarcinoma compared with 64 of 486 (13%) in the over 50 age group.

The estimated overall five year survival was 54% (95% confidence interval, 49.4% to 58.6%). There were no significant differences between the survivals among the various tumour categories (table 5).

The estimated relative risk for patients with category 4 tumours (mucinous adenocarcinoma predominating) compared with patients with non-mucinous tumours (category 1) was exp (0.119) = 1.13 (95% confidence interval, 0.69 to 1.83) (table 6). The values of the estimated relative risks and the corresponding 95% confidence intervals for the other categories of tumour also suggested that the presence of mucinous areas has little or no indepen-

Table 4 Histological categories of tumours and clinicopathological stage in 534 colorectal adenocarcinomas. (Row percentages in parentheses)

Histological category of tumour	Clinicopathological stage				
	Dukes A	Dukes B	Dukes C	Advanced disease*	All stages
1	57 (16)	163 (44)	97 (26)	52 (14)	369
2	12 (14)	42 (48)	23 (26)	10 (12)	87
3	1 (9)	4 (36)	4 (36)	2 (19)	11
4	2 (3)	32 (57)	11 (20)	11 (20)	56
5	0 (0)	4 (36)	4 (36)	3 (28)	11
All tumours	72 (13)	245 (46)	139 (26)	78 (15)	534

*Denotes disease with distant metastases or local growth beyond the surgical margins.

Table 5 *Mean ages, estimated five year survivals, and histological category of tumour in 534 colorectal adenocarcinomas*

Histological category of tumour	Mean age in years (SEM)	Five year survival (95% confidence intervals)
1 (n = 369)	64·6 (0·6)	52·9 (47·5 to 58·3)
2 (n = 87)	65·4 (1·1)	51·6 (40·2 to 63·0)
3 (n = 11)	68·7 (2·7)	77·5 (49·3 to 100)
4 (n = 56)	68·7 (1·5)	60·0 (46·4 to 73·6)
5 (n = 11)	71·0 (2·4)	50·0 (15·6 to 84·4)
All cases (n = 534)	65·4 (0·6)	54·0 (49·4 to 58·6)

dent prognostic influence with the exception of the signet ring cell category in which the relative risk was similar to that of poorly differentiated tumours.

Discussion

In the present series of 534 resected specimens 69 (13%) of the tumours contained mucinous areas that seemed to account for most of the tumour mass. This proportion confirms recent reports in which mucinous carcinomas were defined as tumours containing at least 60–80% mucin by volume, and in which the proportions of such tumours were in the range 10–15%.[5-7 10 17] Altogether, 165 (31%) of the tumours in this study contained some areas showing the characteristic features of mucinous adenocarcioma. Similar proportions (27% and 28%) were found by Hultborn[18] and Pihl et al [6] whereas Minsky et al [17] found only 19% of tumours containing mucin. The comparatively good agreement between various studies about the proportions of mucinous tumours probably indicates

Table 6 *Regression coefficients, relative death risks, and 95% confidence intervals*

Variable	Regression coefficient (SEM)	Expected coefficient (95% confidence intervals)
Sex	0·158 (0·133)	1·17 (0·90 to 1·53)
Age (years)	0·010 (0·006)	1·01 (1·00 to 1·02)
Tumour site:		
Left colon v right colon	0·728 (0·227)	2·07 (1·32 to 3·26)
Rectum v right colon	1·306 (0·226)	3·69 (2·35 to 5·80)
Stage:		
Dukes' B v Dukes' A	0·891 (0·277)	2·44 (1·40 to 4·24)
Dukes' C v Dukes' A	1·527 (0·280)	4·61 (2·63 to 8·06)
Advanced disease v Dukes' A	2·189 (0·296)	8·92 (4·93 to 16·14)
Histological category of tumour:		
Category 2 v 1	0·086 (0·179)	1·09 (0·76 to 1·56)
Category 3 v 1	− 1·381 (0·717)	0·25 (0·06 to 1·05)
Category 4 v 1	0·119 (0·244)	1·13 (0·69 to 1·83)
Category 5 v 1	1·456 (0·473)	4·29 (1·67 to 11·05)
Histological grade of tumour:*		
Moderate v well differentiated	0·559 (0·167)	1·75 (1·25 to 2·44)
Poor v well differentiated	1·420 (0·220)	4·14 (2·66 tc 6·42)

*Based upon the predominating grade.

that these tumours have a highly characteristic histological appearance; this is also shown in the present series by histological reproducibility, which was better than chance expectation. We also confirmed several other reports in finding a more proximal distribution of the mucinous than of the non-mucinous adenocarcinomas throughout the large intestine.[5 7 8 17 18]

Some authors have reported a preponderance of mucinous adenocarcinomas in men,[3 5 8] whereas others have been unable to find any differences between the sexes.[7] In the present study the comparative incidences of tumours with a mucinous component were not significantly different between men and women. Contrary to several other authors,[6-8] we found a higher incidence of mucinous tumours in older than in younger patients. Wolfmann et al found no significant age differences.[3]

Because of their mucinous content, mucinous adenocarcinomas have been thought to have a special propensity for disseminated spread—for example, along tissue planes. The view that such tumours behave more aggressively and have a poorer prognosis has, however, been based mainly on studies in which multivariate analyses have not been used.[3-7 17 19] Berg and Godwin[8] found that mucinous and non-mucinous adenocarcinomas had almost identical prognoses when compared by stages. In a recent large multivariate analysis of mucinous carcinomas of the rectum, Sasaki et al [10] found that large mucinous areas were of no independent prognostic value, despite the extremely poor outcome associated with signet ring cell cancers. In the present series also signet ring cell carcinomas had the poorest prognosis, and our results suggest that this histological type represents an independent explanatory variable. Of the 534 tumours in this study, 11 (2%) were classified as signet ring cell carcinomas compared with less than 1% in several recent studies.[5 10 17]

Sasaki et al [10] reported that mucinous and signet ring cell carcinomas tended to present at a more advanced stage. In accordance with this observation it was noteworthy in the present series that whereas 15% of the non-mucinous tumours were Dukes' A lesions, only 3% of the tumours with a predominantly mucinous component were confined to the intestinal wall. The observed association between increasing amount of mucin and advancing stage may be of value in the histological interpretation of preoperative biopsy specimens from colorectal cancers, although little is known about the pattern of distribution of the mucinous components in the superficial and deep parts of these tumours.

Because of the small number of tumours in some of the categories in this study the results must be interpreted with some reservation as indicated by the wide 95% confidence intervals for some of the regres-

sion coefficients. None the less, the results of the study suggest that when important prognostic factors such as site of tumour, stage, and grade are adjusted for, the presence of mucinous components probably does not imply a poorer prognosis in colorectal cancer unless the predominating tumour component is represented by signet ring cell carcinoma.

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