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Duration of symptoms, stage at diagnosis and relative survival in colon and rectal cancer

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ABSTRACT

In colorectal cancer, the relation between duration of symptoms and stage at presentation and prognosis is not yet settled. All 1263 patients treated for colorectal cancer at Levanger Hospital, 1980–2004, and 2892 patients treated in Norway during 2004 were included. The association between symptom duration as an explanatory variable and tumour stage as a dependent variable was analysed using a proportional odds logistic regression model. Known duration of symptoms was divided into four categories: <1 week, 1–8 weeks, 2–6 months and >6 months. There was an inverse relationship between symptom duration and colon cancer TNM-stage, OR = 0.73 (95% CI 0.63–0.84), $p < 0.001$ (Levanger Hospital) and 0.84 (0.75–0.95), $p = 0.004$ (Norway 2004), where the OR is per category of symptom duration. Duration of symptoms were also inversely associated with T-stage, N-stage and M-stage in colon cancer. These relationships were not found for rectal cancer. In colon cancer the relative five-year survival for the four intervals of symptom duration was 44%, 39%, 54% and 66%, $p < 0.001$, in Levanger, 1980–2004, and four-year survival was 46%, 62%, 75% and 74%, $p < 0.001$, in Norway 2004, respectively. For rectal cancer survival was not dependent on symptom duration. In a multivariate analysis of relative survival of patients with colon cancer, duration of symptoms was associated with survival independent of tumour differentiation and TNM-stage. Increasing duration of symptoms was positively associated with less advanced disease and better survival in colon cancer, but not in rectal cancer.

1. Introduction

Early detection and treatment of colorectal cancer are important as advanced stages have poorer prognosis. It is easy to assume that long duration of symptoms might be associated with more advanced disease at diagnosis and a more serious prognosis. However, for decades, studies have shown either no relationship between duration of symptoms and outcome or that patients with long duration of symptoms have better prognosis.[1–7] This also applies to other forms of cancer. Previous studies have indicated an inverse relationship between duration of symptoms and survival for gastric cancer,[8,9] renal pelvic and ureteral cancer,[10] bladder cancer,[11] extremity or flank sarcoma[12] and in selected lung cancers.[13–15]

In a recent meta-analysis, Ramos et al.[6,16] showed that for cancer of the colon there was an inverse relationship between

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duration of symptoms and stage of the disease, while for rectal cancer less delay was associated with the earlier stages. The results from that meta-analysis were based on available literature from 1965 to 2006 and comprised 5209 patients. The meta-analysis was hampered by small sample sizes and methodological problems in the studies being reviewed. The authors asked for more studies dealing with this issue with larger and unrestricted samples. The present study was therefore done to clarify the relationship between duration of symptoms and TNM-stage, degree of tumour differentiation and relative survival in colon and rectal cancer patients separately.

2. Patients and method

The study was designed to meet the selection criteria used by Ramos et al.[16]

Study setting: Two populations were used. The most detailed data set available came from Levanger Hospital, which is a single institution serving 87,000 people in a defined geographical area. The cohort comprised all 869 colon cancer patients and 394 rectal cancer patients from 1980 to 2004, a total of 1263 patients. The second population included in this study was all cases of colorectal cancer diagnosed in Norway in 2004. In the national cohort, the date of start of treatment was missing in 601 patients. The remaining cohort comprised 2892 patients, 2043 with colon cancer and 849 with rectal cancer. A histological confirmation of the diagnosis was present in 94.4% of the patients from Levanger 1980–2004 and 99.9% of the national cohort from 2004.

Tumour site: Tumours localised in colon and rectum, were included; squamous cell anal carcinomas were excluded. At Levanger Hospital, rectum was defined as up to and including 15 cm from the anal verge, measured by rigid proctoscopy, while for the national cohort rectum was defined as up to 20 cm, in accordance with a more than 50-year continuous tradition at The Cancer Registry of Norway.

Study end-points: The primary study end-point was relative survival. The beginning time point of survival was the first date of treatment. Relative survival was defined as the rate of observed survival rate in the patients to the survival rate expected in a group of people in the general Norwegian population of the same age and gender. Secondary study end-points were T-stage, N-stage, M-stage, TNM-stage and tumour differentiation. Data on bowel obstruction and bowel perforation were available from Levanger Hospital. In the national cohort, data on three stages (TNM-stage I and II together, III and IV) and tumour differentiation were available. T-stage and N-stage data were not available separately.

Patient selection: All diagnosed patients were selected for the study. In the patients from Levanger Hospital, cases with neuroendocrine tumours were excluded. Patients were included in the absence of a microscopic examination, if the diagnosis was supported by endoscopy or roentgen examinations. At Levanger Hospital, a microscopic diagnosis was lacking in 71 patients (5.6%). In the national cohort, all cases were deemed as reliable diagnoses of cancer, either histologically or clinically, by The Cancer Registry of Norway.

Information sources: (1) The health records of all patients treated for a colorectal cancer at Levanger Hospital from 1980–2004 were reviewed by the authors on site, E.J., T.H.E. The patients were identified from the hospital patient registry system, and a complete cohort was achieved using data registered at The Cancer Registry of Norway. All variables registered were defined and agreed on by E.J. and T.H.E. before registration began and journals were double checked for interobserver inconsistency. (2) Data from all patients diagnosed in Norway during 2004 and registered at The Cancer Registry of Norway were reviewed. This year was chosen because in 2004 onset of symptoms was asked for in the registration form used by all doctors for the compulsory report to The Cancer Registry of Norway. This report and the corresponding pathology report were the basis for the analyses of the national cohort.

Definition of delay and measures of the time interval: In the data from Levanger Hospital, delay was measured from the onset of symptoms to start of treatment thereby including diagnostic and therapeutic delay. Data concerning onset of symptoms were collected from the hospital medical records or from the referral letter from the primary physician. For many patients, an exact date of onset was not available, but for most of the patients an approximate duration of symptoms was given. Start of treatment was, for the majority of patients, defined as the date of the first cancer related surgical procedure, curative or palliative. For the remaining patients start of other forms of palliative treatment and care was chosen as start of treatment. In the national cohort, time of first surgical procedure was defined as start of treatment, and in accordance with the cohort from Levanger delay was measured as a symptom to treatment interval. Data on onset of symptoms were obtained from the compulsory report to The Cancer Registry of Norway. The Levanger Hospital data set was categorised in four predefined intervals: <1 week, 1–8 weeks, 2–6 months and >6 months. In the data from The Cancer Registry of Norway, the delay was recorded as a continuous variable, but in this study it was categorised into the same four intervals as in the data set from Levanger Hospital.

Stage classifications: Data from Levanger Hospital were classified according to the TNM-system (6th edition).[17] Data from The Cancer Registry of Norway were based on a classification used at the institution for many decades: localised, regional, distant and unknown.[18]

2.1. Statistical methods

The association between symptom duration as an explanatory variable and tumour stage as dependent variable was analysed using a proportional odds logistic regression model, also called ordinal logit model, as recommended by Agresti.[19] This model allows the explanatory variable to be regarded as a categorisation of an underlying (latent) continuous variable,[19] in this study symptom duration. The resulting OR is a common OR estimate for any 2×2 table that would occur if the $r \times c$ table was collapsed to a 2×2 table along any cut-off thresholds in columns and rows. We have not used a correlation coefficient because it is regarded as less useful for tables that are highly discrete and unbalanced.[19]

Relative survival was estimated using actuarial methods in STATA, according to the methods recommended by Dickman and Coviello[20] The Ederer II method was used for estimating expected survival.[20] Significance tests of excess mortality were done using a maximum likelihood approach. Norwegian population survival probabilities for every year beginning in 1980 and sorted by sex and age were downloaded from the Human Mortality Database.[21] Data were missing for three recent years, and according to standard practice[20] we assumed that the probabilities for the years 2006, 2007 and 2008 were the same as for 2005. Estimates were accompanied by 95% confidence intervals (CI).

Two-sided p-values < 0.05 were considered significant. The analyses were performed using SPSS 15.0 and STATA 10.

3. Results

The duration of symptoms for colon and rectal cancer in each of the two populations is presented in Table 1. There was a trend towards longer duration of symptoms in the colon cancer patients from Levanger compared with the duration in the national cohort $p < 0.001$. The corresponding distributions for rectal cancer were almost equal, $p = 0.55$.

3.1. Duration of symptoms versus stage

The duration of symptoms was inversely associated with T-stage, N-stage and M-stage in colon cancer (Table 2). For rectal cancer there was no significant association between delay and the T-stage, N-stage and M-stage (Table 3). However, there was an interesting tendency of more T-1 and T-2 tumours and less N-1 and N-2 in the 1–8 weeks duration of symptoms. Likewise, the duration of symptoms was inversely associated with the overall TNM-stages in colon cancer (Table 4). In rectal cancer there was no association between duration of symptoms and stage (Table 5).

3.2. Duration of symptoms versus differentiation

Tumour differentiation was significantly related to survival with a univariate hazard ratio of 3.0 (1.0–8.8) for colon cancers with moderate differentiation and 6.6 (2.2–19.8) for tumours with low differentiation in the national cohort. The corresponding hazard ratios for Levanger Hospital were 1.4 (0.8–2.3) and 3.6 (2.0–6.1). However, there was no significant relationship between the duration of symptoms and the differentiation of the tumour for colon cancer at Levanger Hospital, OR = 0.9 (0.8–1.2), $p = 0.89$. Differentiation was uniformly distributed regardless of symptom duration. For rectal cancers there was a tendency towards more well differentiated and less moderate differentiated cancers in patients with symptom duration of <1 week. However, there was no association between symptom duration and differentiation overall, OR = 0.8 (0.6–1.2), $p = 0.35$.

As with the national cohort, no association was found between the duration of symptoms and the differentiation of colon cancers, OR = 0.9 (0.8–1.1), $p = 0.30$, or rectal cancers, OR = 1.3 (0.9–1.7), $p = 0.16$.

3.3. Duration of symptoms versus relative survival

Tables 6 and 7 show the results of multivariate analysis of relative survival of patients with colon cancer treated in Levanger and Norway. When we adjusted for the effect of TNM-stage and grading, the adjusted hazard ratios still decreased as duration of symptoms increased. Patients with missing values for either differentiation of tumour or stage were excluded from these tables. When these patients were included (available case analysis) in an unadjusted analysis of colon cancer patients, the relative five-year survival for the four intervals of symptom duration was 44% (28–62), 39% (31–48), 54% (48–61) and 66% (57–74) in Levanger, 1980–2004, and four-year survival was 46% (35–58), 62% (56–68), 75% (70–80) and 74% (66–81)in Norway 2004, respectively. The small decreases in relative survival compared to those shown in Table 6 and 7 were probably due to the inclusion of patients with more advanced disease.

In a subgroup analysis of the cohort from Levanger 112 patients with acute colon obstruction and 44 with colon perforation were excluded. When patients with these surgical emergencies were excluded, the unadjusted, relative survival increased and was 51% (40–62), 58% (51–65) and 70% (61–78) for 0–8 weeks, 2–6 months and >6 months of symptom duration, respectively. Figs. 1 and 2 show the relative survival in relation to the duration of symptoms for all patients with colon cancer at Levanger Hospital, 1980–2004, and for Norway, 2004.

Relative survival in relation to duration of symptoms was also analysed for rectal cancer. At Levanger Hospital the relative survival was 49% (33–64), 56% (46–64) and 60% (49–69) for 0–8 weeks, 2–6 months and >6 months of symptoms duration,

Table 1 – Duration of symptoms for patients with colon and rectal cancer. The duration was calculated from the time of the first symptoms until the first date of treatment. Number of patients (percent of total, excluding unknown).

Duration of symptoms	Patients from Levanger Hospital 1980–2004		Patients from Norway 2004	
	Colon cancer	Rectal cancer	Colon cancer	Rectal cancer
<1 week	55 (6.6)	9 (2.3)	123 (9.4)	11 (1.9)
1–8 weeks	203 (24.2)	57 (14.6)	425 (32.3)	98 (16.7)
2–6 months	345 (41.1)	176 (45.1)	513 (39.0)	266 (45.3)
>6 months	236 (28.1)	148 (38.0)	254 (19.3)	212 (36.1)
Total known	839 (100)	390 (100)	1315 (100)	587 (100)
Unknown	30	4	728	262
Total	869	394	2043	849

Table 2 – Relationship between duration of symptoms and T-stage, N-stage and M-stage for colon cancer treated at Levanger Hospital 1980–2004. Number of patients (percent).

TNM-stage	Duration of symptoms, Levanger Hospital 1980–2004					
	<1 week	2–8 weeks	2–6 months	>6 months	Unknown	Total
T-1	2 (3.6)	7 (3.5)	19 (5.5)	18 (7.6)	7 (23.3)	53 (6.1)
T-2	4 (7.3)	6 (3.0)	27 (7.8)	22 (9.3)	3 (10.0)	62 (7.1)
T-3	29 (52.7)	116 (57.1)	201 (58.3)	133 (56.4)	12 (40.0)	491 (56.5)
T-4	19 (34.6)	51 (25.1)	76 (22.0)	54 (22.9)	4 (13.3)	204 (23.5)
Unknown	1(1.8)	23 (11.3	22 (6.4)	9 (3.8)	4 (13.3)	59 (6.8)
Total	55 (100)	203 (100)	345 (100)	236 (100)	30 (100)	869 (100)
N-0	19 (34.55)	80 (39.4)	181 (52.5)	140 (59.3)	20 (66.7)	440 (50.6)
N-1	26 (47.27)	50 (24.6)	85 (24.6)	46 (19.5)	2 (6.7)	209 (24.1)
N-2	1 (1.8)	31 (15.3)	27 (7.8)	17 (7.2)	2 (6.7)	78 (9.0)
Unknown	9 (16.4)	42 (20.7)	52 (15.1)	33 (14.0)	6 (20)	142 (16.3)
Total	55 (100)	203 (100)	345 (100)	236 (100)	30 (100)	869 (100)
M-0	45 (81.8)	130 (64.0)	253 (73.3)	189 (80.1)	25 (83.3)	642 (73.9)
M-1	10 (18.2)	73 (36.0)	92 (26.7)	47 (19.9)	5 (16.7)	227 (26.1)
Total	55 (100)	203 (100)	345 (100)	236 (100)	30 (100)	869 (100)

Association between known T-stage and duration of symptoms: OR = 0.8 (0.7–0.9), $p = 0.006$.
Association between known N-stage and duration of symptoms: OR = 0.7 (0.6–0.8), $p < 0.001$.
Association between M-stage and duration of symptoms: OR = 0.8 (0.7–0.97), $p = 0.023$.

Table 3 – Relationship between duration of symptoms and T-stage, N-stage and M-stage for rectal cancer in Levanger 1980–2004. Number of patients (percent).

TNM-stage	Duration of symptoms					
	<1 week	1–8 weeks	2–6 months	>6 months	Unknown	Total
T-1	2 (22.2)	5 (8.8)	12 (6.8)	10 (6.8)	2 (50)	31 (7.9)
T-2	0	12 (21.1)	32 (18.2)	19 (12.8)	1 (25)	64 (16.2)
T-3	3 (33.3)	19 (33.3)	78 (44.3)	72 (48.6)	0	172 (43.7)
T-4	1 (11.1)	17 (29.8)	43 (24.4)	42 (28.4)	1 (25)	104 (26.4)
Unknown	3 (33.3)	4 (7.0)	11 (6.3)	5 (3.4)	0	23 (5.8)
Total	9 (100)	57 (100)	176 (100)	148 (100)	4 (100)	394 (100)
N-0	0	27 (47.4)	85 (48.3)	75 (50.7)	1 (25)	188 (47.7)
N-1	0	9 (15.8)	35 (19.9)	37 (25.0)	1 (25)	82 (20.8)
N-2	2 (22.2)	3 (5.3)	17 (9.7)	14 (9.5)	0	36 (9.1)
Unknown	7 (77.8)	18 (31.6)	39 (22.2)	22 (14.9)	2 (50)	88 (22.3)
Total	9 (100)	57 (100)	176 (100	148 (100)	4 (100)	394 (100)
M-0	6 (66.7)	46 (80.7)	140 (79.5)	118 (79.7)	4	314 (79.7)
M-1	3 (33.3)	11 (19.3)	36 (20.5)	30 (20.3)	0	80 (203)
Total	9 (100)	57 (100)	176 (100	148 (100)	4 (100)	394 (100)

Association between known T-stage and duration of symptoms: OR = 1.2 (0.9–1.5), $p = 0.20$.
Association between known N-stage and duration of symptoms: OR = 1.0 (0.8–1.4), $p = 0.79$.
Association between M-stage and duration of symptoms: OR = 1.0 (0.7–1.3), $p = 0.75$.

respectively. Although survival increased with increasing symptom duration, no significant relationship between delay and survival was found. In the national cohort the opposite trend was found: survival of 81% (68–91), 79% (71–75) and 72% (63–80) for the same three intervals of symptom duration. However, as for the cohort at Levanger Hospital, there was no significant association between symptom duration and survival.

4. Discussion

This report includes 4155 patients, making it the largest single study published to explore the relationship between duration of symptoms and stage and survival in cancer of the colon and the rectum separately. In patients treated for colon cancer at Levanger Hospital during 1980–2004, long duration of symptoms was associated with earlier stages and better relative survival. In patients treated for rectal cancer no such relationship was found. The same applied to colon cancer in a cohort comprising all patients treated for colon and rectal cancer in Norway during 2004. In the national cohort there was a trend towards earlier stages at presentation in rectal cancer patients with short duration of symptoms. This was in agreement with the meta-analysis performed by Ramos et al.[16] concerning colon and rectal cancer.

Table 4 – Relationship between duration of symptoms and stage for colon cancer. Number of patients (percent).

TNM-stage	<1 week	2–8 weeks	2–6 months	>6 months	Unknown	Total
Duration of symptoms, Levanger Hospital 1980–2004						
I	4 (7.3)	10 (4.9)	38 (11.0)	33 (14.0)	9 (30.0)	94 (10.8)
II	15 (27.3)	60 (29.6)	125 (36.2)	100 (42.4)	11 (36.7)	311 (35.8)
III	21 (38.2)	43 (21.2)	76 (22.0)	41 (17.4)	3 (10.0)	184 (21.2)
IV	10 (18.2)	73 (36.9)	92 (26.7)	47 (19.9)	5 (16.7)	227 (26.1)
Unknown	5 (9.1)	17 (8.4)	14 (4.1)	15 (6.4)	2 (6.7)	53 (6.1)
Total	55 (100)	203 (100)	345 (100)	236 (100)	30 (100)	869 (100)
Duration of symptoms, Norway 2004						
I–II	53 (43.1)	197 (46.4)	277 (54.0)	139 (54.7)	407 (55.9)	1073 (52.5)
III	38 (30.9)	135 (31.8)	126 (24.6)	63 (24.8)	164 (22.5)	526 (25.7)
IV	31 (25.2)	89 (20.9)	99 (19.3)	47 (18.5)	116 (15.9)	382 (18.7)
Unknown	1 (0.8)	4 (0.9)	11 (2.1)	5 (2.0)	41 (5.6)	62 (3.0)
Total	123 (100)	425 (100)	513 (100)	254 (100)	728 (100)	2043 (100)

Association between known stage of colon cancer at Levanger Hospital and known duration of symptoms: OR = 0.7 (0.6–0.8), $p < 0.001$.
Association between known Stage of colon cancer in Norway 2004 and known duration of symptoms: OR = 0.8 (0.8–0.95), $p = 0.004$.

Table 5 – Relationship between duration of symptoms and stage for rectal cancer. Number of patients (percent).

TNM-stage	<1 week	2–8 weeks	2–6 months	>6 months	Unknown	Total
Duration of symptoms, Levanger Hospital 1980–2004						
I	0	12 (21.1)	31 (17.6)	23 (15.5)	1 (25)	67 (17.0)
II	0	11 (19.3)	48 (27.3)	49 (33.1)	0	108 (27.4)
III	1 (11.1)	12 (21.1)	43 (24.4)	38 (25.7)	1 (25)	95 (24.1)
IV	3 (33.3)	11 (19.3)	36 (20.5)	30 (20.3)	0	80 (20.3)
Unknown	5 (55.6)	11 (19.3)	18 (10.2)	8 (5.4)	2 (50)	44 (11.2)
Total	9 (100)	57 (100)	176 (100)	148 (100)	4 (100)	394 (100)
Duration of symptoms, Norway 2004						
I–II	6 (54.5)	54 (55.1)	133 (30.0)	88 (41.5)	151 (57.6)	432 (50.9)
III	4 (36.3)	28 (28.6)	81 (30.5)	70 (33.0)	63 (24.0)	246 (29.0)
IV	1 (9.1)	14 (14.3)	38 (14.2)	35 (16.5)	20 (7.6)	108 (12.7)
Unknown	0	2 (2.0)	14 (5.3)	19 (9.0)	28 (10.7	63 (7.4)
Total	11 (100)	98 (100)	266 (100)	212 (100)	262 (100)	849 (100)

Association between known Stage of rectal cancer at Levanger Hospital 1980–2004 and known duration of symptoms: OR = 0.9 (0.7–1.2), $p = 0.559$.
Association between known Stage of rectal cancer in Norway 2004 and known duration of symptoms: OR = 1.2 (0.98–1.5), $p = 0.072$.
TNM-stages I and II were not given separately in the national data.

In this study delay was measured as time from onset of symptoms to start of treatment. This timeframe was chosen because start of surgical treatment had been registered at The Cancer Registry of Norway and date of operation or start of palliative care was obtainable from the medical journals at Levanger Hospital. However, start of treatment is a heterogeneous point and is potentially biased by both diagnostic delay and therapeutic delay. The therapeutic delay could have been avoided by using the symptom to diagnosis interval. Unfortunately at Levanger Hospital pathological confirmation was lacking in 5.6% of the cases. Furthermore, a pathological confirmation ranged from one to six weeks after biopsy, which also makes this a heterogeneous point. The symptom to treatment interval is subject to non-differential bias, but since the study used data from large unrestricted samples of defined populations receiving free health care, the risk of differential bias should be minimal. The more serious problem with this definition of delay is that in general patients who receive palliative surgery have longer delays before surgery. This could potentially assign patients with worse prognosis to longer delays, but if this was the case it would only strengthen the contrary findings of this study.

Whether a study is done retrospectively or prospectively, the variable 'date of first symptom' involves a retrospective question for the patient. However, in a retrospective study the possibility of directly interviewing the patient is lost making this date more uncertain. Information on the duration of symptoms was lacking in one third of the national cohort, while at Levanger Hospital the number with unknown duration was negligible. An explanation for this difference could be that it was easier to allocate patients to one of four time intervals, as is done in Levanger, than to indicate a certain date of symptom onset, as was required by The Cancer Registry of Norway. The first symptom is often vague and difficult or impossible to remember for the patient. Colon cancer, especially when located proximally, may cause occult bleeding with slowly worsening anaemia and insidious symptoms. It is easier for the patient to remember the onset of other symptoms, like macroscopic bleeding from a rectal cancer.

Table 6 – Results of multivariate analysis of relative survival of patients with colon cancer treated at Levanger Hospital 1980–2004.

	No. (%) $n = 760$	Unadjusted hazard ratio	p	Five-year estimated relative survival	Adjusted[a] hazard ratio	p
Duration of symptoms			<0.001			0.002
<1 week	50 (6.6)	1		49% (31–67)	1	
1–8 weeks	180 (23.7)	1.2 (0.8–2.1)	0.84	43% (33–52)	1.0 (0.6–1.6)	0.99
2–6 months	315 (41.5)	0.6 (0.4–1.0)	0.065	58% (51–65)	0.6 (0.4–1.0)	0.055
>6 months	215 (28.3)	0.4 (0.2–0.8)	0.001	70% (61–79)	0.6 (0.4–1.0)	0.033
Differentiation of tumour			<0.001			<0.001
Good	72 (9.5)	1		66% (51–80)	1	
Moderate	526 (69.2)	1.4 (0.8–2.3)	0.22	62% (57–68)	1.1 (0.7–1.8)	0.77
Low	162 (21.3)	3.6 (2.0–6.1)	<0.001	37% (28–47)	1.6 (0.96–2.7)	0.071
Stage			<0.001			<0.001
I	83 (10.9)	1		101%(88–111)	1	
II	300 (39.5)	4.42 (1.1–17.9)	0.037	82% (74–89)	4.3 (1.0–18.0)	0.049
III	181 (23.8)	10.7 (2.7–43)	0.001	58% (49–67)	8.9 (2.1–37)	0.003
IV	196 (25.8)	125 (32–488)	<0.001	0.6% (0–3)	103 (25–422)	<0.001

a Adjusted for all three factors.

Table 7 – Results of multivariate analysis of relative survival of patients with colon cancer treated in Norway 2004.

	No. (%) $n = 1155$	Unadjusted hazard ratio	p	Four-year estimated relative survival	Adjusted[a] hazard ratio	p
Duration of symptoms			<0.001			<0.001
<1 week	111 (9.6)	1		42% (30–54)	1	
1–8 weeks	370 (32.0)	0.5 (0.3–0.7)	<0.001	62% (55–68)	0.7 (0.5–1.0)	0.057
2–6 months	456 (39.5)	0.3 (0.2–0.4)	<0.001	76% (70–81)	0.5 (0.4–0.7)	<0.001
>6 months	218 (18.9)	0.3 (0.2–0.4)	<0.001	77% (68–84)	0.5 (0.3–0.7)	<0.001
Differentiation of tumour			<0.001			<0.001
Good	58 (5.0)	1			1	
Moderate	829 (71.8)	3.0 (1.0–8.8)	0.05	72% (68–76)	1.7 (0.7–4.2)	0.22
Low	268 (23.2)	6.6 (2.2–20)	0.001	52% (44–59)	3.0 (1.2–7.3)	0.017
Stage			<0.001			<0.001
I–II	596 (51.6)	1			1	
III	329 (28.5)	4.0 (2.6–6.1)	<0.001		3.3 (2.2–4.9)	<0.001
IV	230 (19.9)	21 (14–31)	<0.001		16 (11–24)	<0.001

a Adjusted for all three factors.

We chose to define the beginning time point of survival as the first date of treatment. As both diagnostic and therapeutic delays are included in the symptom to treatment interval, a lead time bias could occur: confusing rapid diagnostics and treatment with increased survival. Despite this, in the present study the contrary was found; longer delays were not associated with more adverse stages or shorter survival. Furthermore, the twofold increase in four- and five-year relative survival rates observed in colon cancer with longer delays could not be explained simply by a few months differences in symptom duration.

Coloncarcinogenesis involves multiple steps over decades of time.[22] Most of this time the cancer is asymptomatic, and it may seem reasonable to assume that a therapeutic delay of weeks or a few months could have little effect on the outcome. Nevertheless, an inverse relationship between duration of symptoms and stage and relative survival in colon cancer seems to be a paradox. One might speculate that aggressive tumours in some way are accompanied by other and more alarming symptoms than less aggressive tumours. It has been shown[23] that serious symptoms, such as pain, reduce delay in patients with colorectal cancer.

The differentiation of the tumour is an indicator of aggressiveness.[24] We had a hypothesis that 'aggressive' tumours might give stronger symptoms, which would lead to shorter delay before treatment. Along the same lines, we expected that tumours in patients with shorter delay would be less differentiated than tumours in patients with longer delay. We did not find such an association. On the other hand, in the present multivariate analysis of variables related to survival, duration of symptoms remained a significant variable after controlling for stage and grade of the disease. The aggressiveness might be better characterised in genetic and proteomic analysis.[25]

The present study found a difference between cancers of the colon and rectum concerning the influence of duration

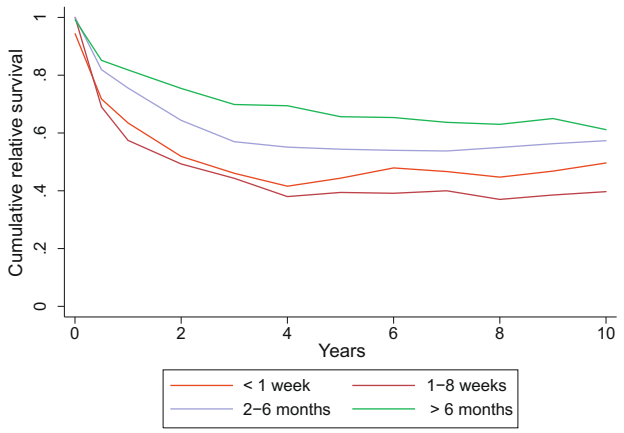

Fig. 1 – Relative survival in patients with colon cancer treated at Levanger Hospital 1980–2004 in relation to duration of symptoms.

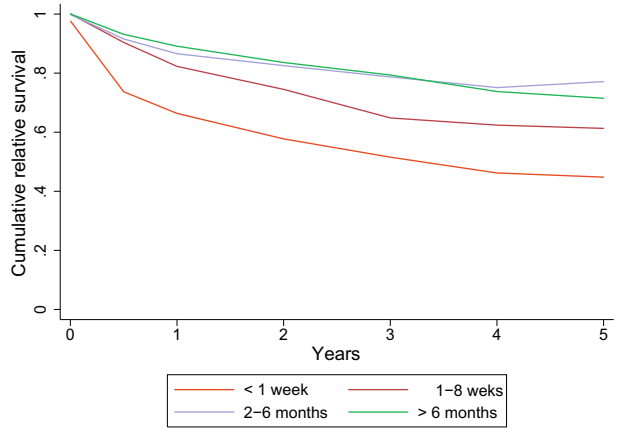

Fig. 2 – Relative survival in patients with colon cancer treated in Norway in 2004 in relation to duration of symptoms.

of symptoms upon the prognosis. Although we could only find an insignificant trend towards worse prognosis for patients with a rectal cancer and long duration of symptoms, others have found a significant positive relationship.[26] It has recently been shown[27] that a significant proportion of rectal cancers may arise via an alternative pathway to the Vogelstein model.[28] It is important to assess cancers of the rectum and colon separately when evaluating the effect of symptoms duration.[6]

Colon cancer presented as an emergency has a more serious prognosis.[29–31] The association between short duration of symptoms and a serious prognosis in colon cancer might possibly be explained by the impact from this emergency group. However, after having excluded patients with acute colon obstruction or perforation, a trend towards shorter survival in colon cancer patients with short duration of symptoms was still apparent.

According to Rupassara et al.,[32] 'attempts to speed up further the diagnosis based on symptoms would be a waste of time and resources, being unlikely to make an appreciable difference to the overall cure rate'. Smith et al.[33] increased the detection of early (Dukes A) cancers to 30% by utilising a computer system with a comprehensive history of bowel symptoms and related factors. For each patient a weighted numerical score was calculated. To detect colorectal cancer in its asymptomatic phase and thereby reduce the mortality, mass screening using faecal occult blood test and colonoscopy in positive cases is effective.[34] The impact of mass screening is related to good planning and organisation and the ability to ensure safe procedures.[35] Screening may become an important addition to public awareness of cancer alarm symptoms.[4] Screening for familial cancer should have priority over screening in low risk groups. One important issue in mass screening is that the capacity for endoscopy is restricted because of limited personnel and economic resources.[36] Recent research shows that colonoscopy screening may have low effectiveness for cancer in the right colon.[37,38] The effects of screening in low risk groups must finally be measured in terms of future decreases in mortality and possibly in incidence.[36] In the future, genomic or proteomic analysis may also be of help in the early detection of cancer.[25]

The delay between first symptom and treatment involves many factors that may vary between cultures and countries. They may range from patients' awareness and tolerability of symptoms and signs to the organisation of the health care system. Norway has a well developed health care system with an aim of providing the same health service to all regardless of socioeconomic status or geography. We believe that our results can be extrapolated to other countries with a similar organisation of the health care system. The results of the present study were in accordance with those of the recent systematic review of Western World literature from 1968 to 2006 by Ramos et al.[6,16] This supports the assumption that the findings of the present study may be valid for similar countries, but generalisation to other populations must be done with caution.

5. Conclusion

There is an inverse relationship between symptom duration and prognosis for patients diagnosed with a colon cancer. No significant relationship could be found for rectal cancer. This does not mean that delay of diagnosis for the individual patient is unimportant.

Conflict of interest statement

None declared.

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