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Original Paper

Survival in Small Intestinal Adenocarcinoma

N. Zar,[1] L. Holmberg,[1,2] E. Wilander[3] and J. Rastad[1]

[1]Department of Surgery, University Hospital, Uppsala S-75185; [2]Cancer Epidemiology Unit, University Hospital, Uppsala S-75185; and [3]Department of Pathology, University Hospital, Uppsala S-75185, Uppsala, Sweden

All cases of adenocarcinoma in the duodenum ($n = 263$) and jejunum/ileum ($n = 663$), diagnosed between 1960 and 1988, were recruited from the Swedish Cancer Registry. Corrected and overall survival were investigated by sex, age and year of diagnosis with life-table and Cox proportional hazards analyses. The corrected 5- and 10-year survival rates were 39% and 37% for duodenal tumours and 46% and 41% for those in jejunum/ileum ($P = 0.16$ for difference between sites). The corrected 5- and 10-year survival rates were 52% and 48% for women and 40% and 34% for men with tumours in jejunum/ileum ($P = 0.0095$ for difference by sex) while no such relation was found in duodenal tumours ($P = 0.84$). Survival correlated with age at diagnosis for duodenal tumours ($P = 0.03377$). A Cox proportional hazards analysis revealed a temporal trend with more favourable prognosis in recent years. This study confirms that prognosis of small bowel adenocarcinoma is serious, but gives a more optimistic outlook than many hitherto published series. Copyright © 1996 Elsevier Science Ltd

Key words: small intestine, adenocarcinoma, survival

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INTRODUCTION

MALIGNANT TUMOURS of the small intestine are rare and the two dominating histological types are the carcinoid and adenocarcinoma. Most studies indicate that small intestinal adenocarcinoma has a poor prognosis, although the literature is contradictory in this respect. Reported 5-year-survival (overall and corrected) ranges between 0 and 46% for jejunal/ileal tumours [1–17] and 0 and 30% for duodenal tumours [6, 11, 14, 15, 17–19]. There are few population-based series describing prognosis of small bowel adenocarcinoma and previous survival analyses generally relate to limited hospital populations, collected over substantial periods of time. Exclusion of autopsy diagnoses and origin from the papilla Vateri vary among the available studies as do the quality of statistical analyses. Furthermore, there is little information on prognostic influence of sex and age and it is unknown if survival has improved for cases diagnosed more recently.

Correspondence to L. Holmberg.
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This report represents a population-based, nationwide analysis of 926 adenocarcinomas in the duodenum and jejunum/ileum, which have been studied for corrected and overall survival in relation to age, sex and period of diagnosis.

PATIENTS AND METHODS

All patients with primary adenocarcinoma of the small intestine (histopathological type 096, ICD-VII 152.0–152.9) diagnosed between 1960 and 1988 and reported to the Swedish National Cancer Registry were identified. Only cases in which the diagnosis was made *in vivo* from histological analysis were included into the study, whereby diagnosis incidentally at autopsy as well as by clinical or mere cytological examination were excluded (Table 1). Moreover, tumours of the ampulla of Vater (ICD 155.3) were disregarded. Tumours in jejunum and ileum were treated as one group, and altogether, 263 cases with duodenal lesions and 663 with jejunal/ileal tumours were included. Table 2 shows the patient distribution by sex, age and year of diagnosis.

The National Cancer Registry and Causes of Death Registry

All physicians in Sweden must report every case of diagnosed cancer to the National Cancer Registry. Pathologists

Table 1. Number of cases recruited from the National Cancer Registry and exclusions due to lack of histological diagnosis in vivo

Small intestinal tumours reported to registry	4188
Adenocarcinoma cases excluded	1139
Diagnosis at autopsy	205
Clinical or cytological diagnosis only	8
Adenocarcinoma cases included	926
Tumours in the duodenum	263
Tumours in the jejunum/ileum	663

and cytologists separately report all cancer diagnoses on surgically removed tissues, biopsies, cytological specimens and autopsies [20]. Most cases are thus reported twice [21]. The Causes of Death Registry is based upon death certificates issued by the physician who has examined the dead body (clinical examination, autopsy or forensic necropsy) and it includes the date and causes of death for deceased registered as Swedish residents [22]. The information from the death certificates are merged into the files of the National Cancer Registry supplying date, underlying and contributory causes of death. There is approximately 87% concordance between the classification of causes of death National Cancer Registry and certified underlying causes of death [23]. During this time period less than 3‰ of the whole Swedish population emigrated, and less than 1.5‰ of subjects were older than 40 years. No attempt was made to correct for emigration.

Validity of the Cancer Registry was analysed by review of pathologists' original reports and re-examination of available microscopic slides in a randomised sample of 200 cases of small intestinal adenocarcinoma. Records of 172 (86%) could be retrieved and in 136 cases the slides were also examined. In 21 cases, the pathologist's report could not be found due to closure of hospitals and/or disposal of old archives. There was no answer to our request for the records from three hospitals (5 cases) and another case could not be found due to lack of information on the reporting laboratory and hospital in the National Cancer Registry file. In one case, the reporting laboratory could not be located. Most common causes for disagreement between registries and hospital records were ICD-coding mistakes ($n = 10$) since unequivocal non-small intestinal adenocarcinoma was diagnosed by the reporting pathologist as well as by review of the available records and microscopic slides. In two cases, the lesion was diagnosed incorrectly by the reporting pathologist and in another four, primary tumour sites was equivocal due to massive overgrowth on adjacent organs (Table 3). The misclassifications were not correlated to patient sex, age or period of diagnosis. The misclassified cases from the sample were excluded from further analyses.

Table 2. Distribution by sex, age and period of diagnosis for the patients with adenocarcinoma in the small intestine

	Duodenum ($n = 263$)	Jejunum/ileum ($n = 663$)
Male	130 (49.4%)	338 (51.0%)
Period of diagnosis		
1960–1970	53 (20.2%)	165 (24.9%)
1971–1977	46 (17.5%)	172 (25.9%)
1978–1984	86 (32.7%)	179 (27.0%)
1985–1988	78 (29.7%)	147 (22.2%)
Age group		
0–50	28 (10.6%)	95 (14.3%)
51–59	44 (16.7%)	114 (17.2%)
60–67	61 (23.2%)	140 (21.1%)
68–74	71 (27.0%)	148 (22.3%)
⩾ 75	59 (22.4%)	166 (25.0%)

Table 3. Discordant diagnoses in hospital records compared to the National Cancer Registry file for 172 *examined cases selected at random*

	No.	Comment
Unknown site of primary tumour	4	Incorrect ICD-coding
Colon cancer	3	Incorrect ICD-coding
Carcinoid tumour	2	Incorrect ICD-coding
Tumours of the papilla of Vater	2	Incorrect ICD-coding
Secondaries from colonic carcinoma	1	Incorrect ICD-coding
Neurofibrosarcoma	1	Incorrect ICD-coding
Reticular-cell sarcoma	1	Incorrect ICD-coding
Tumour of endocrine origin	1	Misdiagnosed by pathologist
Lymphoma	1	Misdiagnosed by pathologist
Total	16	

Statistical methods

Overall and corrected survival rates (i.e. small intestinal malignant tumour or malignant tumour of the digestive tract NOS as the main or contributory cause of death) were calculated with life-table methods [24]. The analyses were made by sex, age and year of diagnosis separately for duodenal and jejunal/ileal tumours. Ninety-five per cent confidence intervals of the estimates are given. The log-rank test was utilised to assess differences between survival curves; $P < 0.05$ was considered statistically significant. Cox proportional hazards analysis was used to study the independent effect on survival of each variable [25]. In the Cox models, period of diagnosis was coded with dummy variables using 1960–1970 as reference category. In trend analyses of time-period of diagnosis, the categories were represented as 0 to 3, beginning with 1960–1970. Age at diagnosis was used as a continuous variable.

RESULTS

Overall and corrected survival

The probability of survival rapidly declined in the initial years after diagnosis and subsequently stabilised (Figures 1–3), which also was supported by the modest differences in 5- and 10-year survival rates (Tables 4 and 5). The overall 5- and 10-year survival rates (Figure 1) were 24% and 17% for duodenal tumours, and 28% and 20% for tumours in jejunum/ileum, but the difference in prognosis between the sites was not statistically significant ($P = 0.09$). The corresponding corrected survival rates were 39% and 37% for duodenal tumours and 46% and 41% for those in jejunum/ileum ($P = 0.16$ for difference between sites).

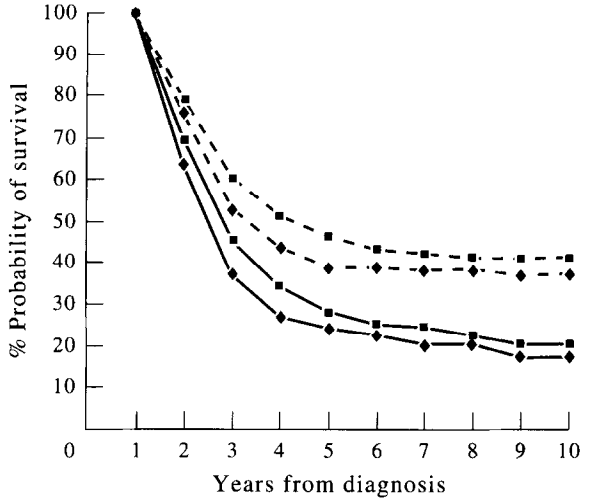

Figure 1. Overall (—) and corrected (- - -) survival rates for patients with adenocarcinoma in the duodenum (◆) ($n = 263$) and jejunum/ileum (■) ($n = 663$).

Influence of sex

Women with tumours in jejunum/ileum showed higher survival rates than men (Figure 2). The 5- and 10-year corrected survival rates were 52% and 48% for women and 40% and 34% for men ($P = 0.0095$ for difference between sexes; Table 4). The relation between sex and corrected survival ($P = 0.84$) was not found for patients with duodenal tumours (Table 5).

Influence of age and time period for diagnosis

Figure 3 presents the age-specific survival curves for duodenal tumours. Corrected survival correlated with age at diagnosis for duodenal tumours ($P = 0.03377$) but not for those in jejunum/ileum ($P = 0.3917$; Tables 4 and 5).

The life-table analyses showed no difference in survival when comparing periods of diagnosis in neither duodenal nor jejunal/ileal tumours ($P = 0.12$ and 0.22, respectively for corrected survival).

The ability of the log-rank test to discriminate for a weak or a moderate trend for differences in survival by age group

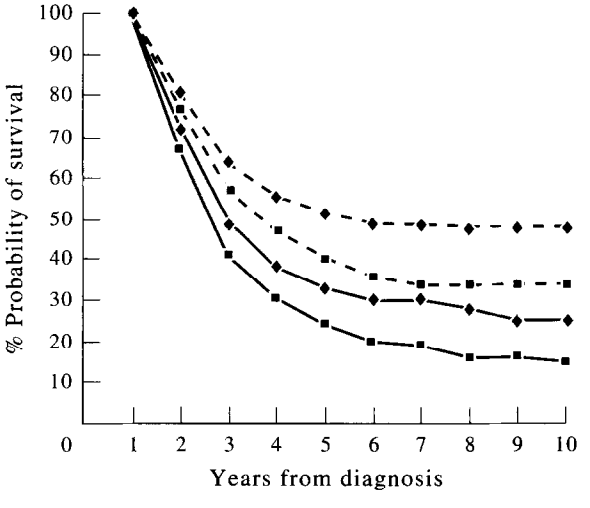

Figure 2. Overall (—) and corrected (- - -) survival rates for male (■) and female (◆) patients with adenocarcinoma in the jejunum/ileum.

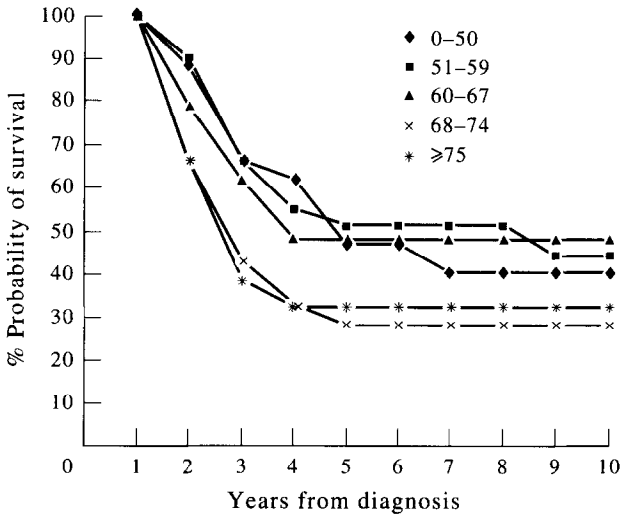

Figure 3. Corrected survival rates for patients of different age intervals (years) at diagnosis of duodenal adenocarcinoma.

or time period of diagnosis is low and we further analysed these and influences by sex and site in Cox proportional hazards models.

Cox proportional hazards models

In the univariate proportional hazards analyses, sex was a statistically significant ($P = 0.04$) predictor of corrected survival for all patients with adenocarcinoma of the small intestine (Table 6). Furthermore, diagnosis later than 1984 was associated with statistically significantly lower estimates of relative hazards ($P = 0.01$). Since the life-table analyses indicated qualitative differences between duodenal and jejunal/ileal tumours, the multivariate analyses were stratified by site. In the multivariate models including gender, period of diagnosis and age at diagnosis, the relative hazards for men with adenocarcinoma in jejunum/ileum was higher ($P = 0.01$) than that for women, while there was no difference by gender ($P = 0.92$) for duodenal tumours (Table 6). Age at diagnosis remained a statistically significant predictor of prognosis in patients with duodenal tumours as the relative hazards increased by 30% with each 10-year increment. The decrease in relative hazards for cases diagnosed in the period 1985–1988 in the univariate model was also found in the multivariate model, although the difference was not formally statistically significant for tumours in jejunum/ileum ($P = 0.06$). Test for trend by time-period revealed clearly statistically significant results in the univariate analysis and in the multivariate analysis for duodenal tumours.

DISCUSSION

Few population-based studies of reasonable size have been presented for small bowel adenocarcinoma [1, 4, 6, 14, 18]. Five-year survival exceeding 25% has not been reported in these series, which is probably attributable to the fact that overall rather than corrected survival rates have been analysed. In selected subgroups of patients with small intestinal adenocarcinoma, some authors have found corrected 5-year survival exceeding 45% [5, 11]. Moreover, detailed analyses of prognostic variables are rare in earlier works. Adler and associates, however, found no difference in corrected 5-year survival between patients below and

Table 4. Probability (%) of corrected and overall survival with 95% confidence limits for jejuno-ileal adenocarcinoma

	Corrected			Overall		
	5-year	10-year	*P* (logrank)	5-year	10-year	*P* (logrank)
Gender						
Male	40(34, 46)	34(28, 41)		24(19, 28)	15(11, 19)	
Female	52(46, 58)	48(41, 54)		33(28, 38)	25(20, 30)	
			0.0095			0.0045
Period						
1960–1970	42(33, 50)	38(29, 46)		26(19, 33)	20(14, 26)	
1971–1977	46(38, 55)	42(33, 51)		27(20, 33)	15(09, 21)	
1978–1984	44(36, 53)	38(29, 46)		27(20, 34)	20(14, 26)	
1985–1988	53(43, 63)			36(27, 44)		
			0.2200			0.1470
Age group						
0–50	52(41, 63)	45(34, 57)		37(27, 47)	31(21, 41)	
51–59	37(26, 47)	33(22, 43)		27(17, 34)	18(11, 27)	
60–67	43(33, 52)	37(26, 47)		26(18, 33)	16(08, 23)	
68–74	52(42, 61)	45(35, 55)		31(23, 38)	23(17, 30)	
⩾75	49(40, 57)	47(38, 56)		25(18, 32)	15(08, 21)	
			0.3917			0.0039

above 65 years of age [1]. There have been no reports of changes in survival over time or of sex as a prognostic variable.

This study took advantage of the population-based National Cancer and Causes of Death Registries in Sweden. Accuracy and completeness of these registries have been carefully investigated in earlier studies. Less than 2% of histologically confirmed cancer cases known from death certificates are missing in the Cancer Registry [21]. Moreover, concordance between Cancer Registry diagnosis and certified causes of death is approximately 87% [23]. When reviewing a randomised sample of the present material, the diagnosis of small intestinal adenocarcinoma could not be verified in 9%. This modest misclassification mostly depended on ICD miscodings and was not associated with the investigated determinants of prognosis. Therefore, the misclassification may have slightly influenced the overall results if tumours with generally better or worse prospects than small intestinal adenocarcinoma selectively had been included. There was no evidence for any strong tendency in either direction. The misclassification should, however, not hamper the comparison between sex, site, time-period or age in other way than making differences more difficult to detect.

If an event in the analysis of corrected survival had been defined only as death of malignant tumour of the small intestine as the underlying cause, survival rates would most probably have been overestimated. However, our current definition may lead to some overestimation since deaths from other, not properly diagnosed intra-abdominal malignancies may be included as events. However, we have no reason to believe that the misclassification is associated with

Table 5. Probability (%) of corrected and overall survival with 95% confidence limits for duodenal adenocarcinoma

	Corrected			Overall		
	5-year	10-year	*P* (logrank)	5-year	10-year	*P* (logrank)
Gender						
Male	38(28, 48)	38(28, 48)		22(15, 30)	19(11, 26)	
Female	40(30, 50)	34(23, 46)		26(18, 34)	14(06, 22)	
			0.8440			0.9441
Period						
1960–1970	27(13, 41)	23(08, 37)		17(07, 27)	08(00, 15)	
1971–1977	36(19, 52)	29(10, 47)		20(08, 31)	10(01, 19)	
1978–1984	43(31, 55)	43(10, 43)		31(21, 41)	27(17, 36)	
1985–1988	49(36, 63)			26(16, 36)		
			0.1208			0.1481
Age group						
0–50	47(23, 68)	40(18, 62)		27(10, 44)	16(01, 33)	
51–59	51(34, 66)	44(25, 63)		38(23, 53)	29(14, 45)	
60–67	48(34, 63)	48(34, 63)		27(15, 39)	22(09, 35)	
68–74	28(15, 40)	28(15, 40)		17(08, 26)	10(02, 19)	
⩾75	32(18, 47)	32(18, 47)		15(06, 24)	08(00, 16)	
			0.03377			0.0005

Table 6. Relative hazards with 95% confidence limits in uni- and multivariate Cox proportional hazards analysis of corrected survival

	Univariate		Multivariate			
	Small bowel	*P*-value	Duodenum	*P*-value	Jejunum/ileum	*P*-value
Male (versus female)	1.2 (0.7, 1.0)	0.04	1.0 (0.7, 1.4)	0.92	1.3 (1.1, 1.7)	0.01
Period						
1960–1970	ref.		ref.		ref.	
1971–1977	0.9 (0.7, 1.0)	0.23	0.7 (0.4, 1.2)	0.26	0.9 (0.7, 1.1)	0.44
1978–1984	0.8 (0.7, 1.1)	0.17	0.6 (0.4, 0.9)	0.03	0.9 (0.7, 1.2)	0.40
1985–1988	0.7 (0.5, 0.9)	0.01	0.5 (0.3, 0.8)	0.01	0.7 (0.5, 1.0)	0.06
Test for trend	$P = 0.02$		Test for trend $P = 0.005$		Test for trend $P = 0.08$	
Age (per 10 years)	1.1 (1.0, 1.1)	0.18	1.3 (1.1, 1.5)	0.002	1.0 (0.9, 1.1)	0.42
Jejunum/ileum (versus duodenum)	0.9 (0.7, 1.1)	0.20				

any of the determinants of prognosis studied, and thus the misclassification should be non-differential. This would mean that, if anything, differences noted here are underestimated.

Women with adenocarcinoma of the jejunum/ileum had better prognosis than men and increased age correlated with poorer prognosis in duodenal but not in jejunal/ileal tumours. The favourable relationship between female sex and survival has been found in a number of epithelial tumours. An explanation proposed for this phenomenon is that female sex hormones have a role in modulating tumour dissemination [26]. The reason for sex not being a prognostic factor in adenocarcinoma of the duodenum is not clear. Hypothetically, it may relate to the higher incidence of peptic ulcer disease among men with greater frequency of endoscopic examinations of the upper gastrointestinal tract, which could facilitate earlier cancer diagnosis.

The survival pattern over follow-up time substantiated high risk of recurrence and/or progression of disease over the first 5–6 years after diagnosis. Thereafter, this risk levelled off, which probably cannot be explained only by small numbers, since altogether 130 patients were effectively observed during the seventh year of follow-up. The survival pattern suggests the existence of a group of long-term survivors with a small risk of progression during the remainder of their lives.

The proportional hazards analysis of corrected survival revealed a temporal trend with decreasing relative hazards in the late eighties as compared to the period 1960–1970. There is no evident explanation for this, although the increased use of endoscopic examination of the upper gastrointestinal tract may have improved survival for some patients. This theory is supported by the more pronounced decrease in relative hazards in cases with duodenal tumours. Improved treatment *per se* is an unlikely course as essentially no new treatment modalities have been introduced. Radiation therapy and chemotherapy have not been systematically evaluated in the treatment of adenocarcinoma of the small intestine.

Taken together, the present study confirms that prognosis is serious in small intestinal carcinoma. However, this population-based material gives a generally more optimistic outlook than hitherto published series. Five to 7 years after diagnosis, approximately 35% of the patients exhibited little risk of disease-related death, and this proportion increased during later time periods. More detailed studies are required to determine clinical and tumour characteristics for these patients and any causes for the temporal trend in their frequency, since these circumstances may provide clues to improved clinical management of small bowel adenocarcinoma.

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