Colorectal cancer: A total provincial experience with survival analysis

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ABSTRACT: A review of 1212 cases of colorectal cancer from the Manitoba Tumour Registry from 1974 through 1976 was done in order to establish survival rates for a total population, to examine the role of tumour differentiation and stage of disease on survival, and to examine the incidence of disease in the rural and urban populations. Stage was the most important factor in determining survival although the difference between stages C₁ and C₂ disease was not significant. However, a continuing relapse rate was seen in all patients with any type of infiltrating disease (B₁ and B₂). There appeared to be continuing relapse patterns in all those groups to at least 96 months. Histology was also an independent predictor of survival even when controlling for stage of disease. Some patients with well differentiated colorectal cancers with stage D disease (over 10%) were alive at 42 months. Age was not found to be a significant factor in survival except for those individuals over 71-years-old and sex was not an important factor. There was increased incidence of colorectal cancer in urban as opposed to rural populations, suggesting that possible differences in lifestyle may play a role in causation. *Can J Gastroenterol* 1989;3(3):126-130

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COLORRECTAL CARCINOMA IS ONE OF the most commonly occurring neoplasms in Canada with 9000 new cases and 5130 deaths in 1979 (1). In view of the many screening studies which are now being done for this disease (2) and the trials of adjuvant therapy which have been reported (3-6), the authors decided to review the total provincial experience in Manitoba to establish certain baselines in order to guide future studies. Several questions were asked in this study: what are the survival rates of colorectal cancer in the total provincial experience and what are the patterns of relapse; does the differentiation of the tumours as reported on the routine pathology records bear prognostic significance; what is the influence of staging on survival; is there a difference in the incidence of the disease in the rural and urban populations which might be a reflection of diet or

Le cancer colorectal: Expérience portant sur une province entière et analyse de survie

RESUME: Une étude portant sur 1212 cas de cancer colorectal tirés du Manitoba Tumour Registry de 1974 à 1976 a été effectuée pour établir le taux de survie d'une population totale; pour examiner le rôle de la différenciation des tumeurs et du stade de la maladie sur la survie; et pour déterminer également l'incidence de la maladie en populations rurales et urbaines. Le stade d'évolution de la maladie était la facteur de survie le plus déterminant bien que la différence entre les stades C_1 et C_2 de la maladie ne soit pas significative. Ce qui est surprenant, par contre, c'est l'index de récidives répétées chez tous les patients souffrant de maladie infiltrante, quel qu'en soit le type (B_1 et B_2). Il semble y avoir des séquences de récidives continues dans tous ces groupes jusqu'à environ 96 mois. Néanmoins, l'histologie permet également de prédire indépendamment la survie même quand le contrôle porte sur le stade de la maladie. Certains cas de cancer colorectal bien différenciés au stade D de la maladie (plus de 10%) étaient en vie à 42 mois. L'âge ne semble pas significatif excepté pour les individus de plus de 71 ans et le sexe n'est pas un facteur important. L'incidence du cancer colorectal est plus élevée en milieu urbain, ce qui laisse entendre que le mode de vie joue peut-être un rôle.

other factors; and is there an influence of age or sex on survival?

METHODS

The Manitoba Tumour Registry is an organization to which all biopsies in the province are reported by law. The authors reviewed all cases of colorectal cancer reported to the registry in a three year period (1974 to 1976) and extracted the following information: age of patients; sex; rural or urban address; therapy (surgery — abdominal, perineal, hemicolectomy, etc); postoperative treatment (radiotherapy, chemotherapy, no treatment); the presence of venous or lymphatic invasion exclusive of known lymph node involvement; differentiation of the tumours as noted by the pathology report; stage of disease by the Astler Collier classification (7) (Table 1); site of the cancer; initial diagnosis; and last

follow-up or death. Deaths from carcinoma were listed as deaths, but deaths from other intercurrent illness were treated as censored information in the life-table analysis plots. If secondary malignance intervened, survival was again calculated up to that time and subsequently censored unless it was clear that death was due to the colon cancer.

Survival rates were determined by the actuarial life-table method (8) and were compared using the Wilcoxon or log-rank statistic (8). To identify the parameters that predict survival, multivariate regression analysis was also carried out. The explanatory variables included histology and stage of disease.

RESULTS

A total of 1212 cases were reviewed. There were 603 males and 609 females. There were 807 cases from urban areas and 405 from rural parts of Manitoba. The population of Manitoba, 1986 census, was 1,071,232 with 664,551 from urban areas. The ratio of urban cancers to the total urban population was 0.0012 and the ratio of rural cancers to the total rural population was 0.00093. The difference between those ratios was significant ($P=0.0002$). The population of Manitoba under the age of 60 years was also studied because older individuals may have moved into the city on retirement and then developed their cancer, thereby inflating the urban numbers.

There were 169 cases of cancer in a population of 511,920 (population under 60) in urban areas and 98 cases out of a population of 367,808 in rural areas (significant difference $P=0.05$). There were 813 cases where Astler Collier staging could be ascertained from chart review (Table 2). Figure 1 displays the life-table survival plots of the groups according to stage. Actuarial mean survival for each stage was as follows: A, 93 months; B_1 , 66 months; B_2 , 48 months; C_1 , 18 months; C_2 , 20 months; and D, six months. There was a significant difference in survival plots for stages A versus B_1 ($P=0.001$), B_1 versus B_2 ($P=0.01$), B_1 versus C_1 ($P=0.001$), B_2 versus C_1 or C_2 ($P=0.01$) and C_2 versus D ($P=0.001$). There was no significant difference between C_1 versus C_2 .

TABLE 2
Astler Collier stages of colorectal cancer at presentation

Stage	Number (%)
A	31 (3.9%)
B_1	92 (11.7%)
B_2	233 (29.7%)
C_1	19 (2.4%)
C_2	232 (29.7%)
D	206 (26.4%)

There was a continuing relapse pattern seen in all stages of disease. The death rate per year in stage B_1 was approximately 5% per year until year 4 when it increased to 10% and maintained, at that rate, with the last death at nine-and-one-half years. The same analysis for B_2 revealed a death rate of 15% for the first year and 20% per year thereafter with the last death at nine-and-one-half years and for C_1 the death rate was 30% yearly for six years and that rate continued to eight years.

Four hundred and forty-five cases could be identified by histologic type and stage. Cancers, if classified in a mixed grade, were analyzed with the poorer prognostic group. Poorly differentiated and anaplastic cancers were analyzed together. Three basic groups were identified: well differentiated, moderately differentiated and poorly differentiated (Table 3). Table 4 lists correlation between histologic grade and stage. Patients with

TABLE 1
Stage of disease by the Astler Collier classification

Dukes A	Confined to mucosa and submucosa
Dukes B_1	Through muscularis, not through serosa, negative nodes
Dukes B_2	To or through serosa or into pericolic fat, negative nodes
Dukes C_1	Not through serosa, positive nodes
Duke's C_2	Through serosa, positive nodes
Dukes D	Distant metastases

Large bowel distal to peritoneal reflection does not have serosal count

well differentiated tumours did not enjoy a better survival than those with moderately differentiated, but both had a better survival than those with poorly differentiated tumours ($P=0.001$) (Figure 2). When comparing the C₂ and D stages in the well differentiated and poorly differentiated groups there was a significant survival difference in favour of the well differentiated group ($P=0.05$ and $P=0.04$, respectively) (Figure 3). There was also a significant difference in the moderately differentiated C₂ and the poorly differentiated C₂ ($P=0.05$). Significance was not reached with the other stages.

TABLE 3
Histologic grade of colorectal cancer

Histologic classification	Number of cases (%)
Well differentiated	129 (29.2%)
Moderately differentiated	233 (52.8%)
Poorly/anaplastic	83 (18.8%)

Stage of disease and differentiation (well differentiated) were confirmed by Cox multiple regression analysis as independent prognostic variables with stage being the most important. Age of patients was also analyzed in terms of percentage, stage and survival. Age and stage of patients at presentation are listed in Table 5. Total survivals were compared along each of the age groups. No difference was found between the survival patterns with the exception of the group older than 71 years at diagnosis who had a significantly shorter survival time, with a large number dying within the first six months. Mean survival times were as follows: younger than 37 years, 23 months; 40 to 51 years, 23 months; 51 to 60 years, 17 months; 61 to 70 years, 23 months; and older than 71 years, six months (Figure 4). Sex of the patient appeared to have no influence on survival. Some patients were given chemotherapy at the oncologists discretion for node positive disease. The authors identified 21 stage C patients with node positive disease and compared their survival with the rest of the C group. The median survival of the chemotherapy (5-fluorouracil) group was

TABLE 4
Correlation between histologic grade and stage

Stages	Well differentiated	Moderately differentiated	Poorly differentiated
A	9 (7.0%)	0 (0%)	1 (1.2%)
B ₁	32 (24.8%)	34 (14.6%)	4 (4.8%)
B ₂	40 (31.0%)	98 (42.1%)	12 (14.5%)
C ₁	2 (1.6%)	7 (3.0%)	5 (6.0%)
C ₂	28 (21.7%)	67 (28.7%)	32 (38.6%)
D	18 (14.0%)	27 (11.6%)	29 (34.9%)
A + B	(31.8%)	(14.6%)	(6.0%)
A,B,B ₂ *	(62.8%)	(56.6%)	(20.5%)

* No nodal metastases

Figure 1) Survival by disease stage

Figure 2) Survival by histology. PD Poorly differentiated; WD Well differentiated; MD Moderately differentiated

TABLE 5
Age and stage of patients at presentation

Age (years)	Percentage of group	A,B,B ₂ percentage	Stages C,C ₂ ,D percentage	D percentage
37 or younger	1.6	20	80	6.7
38 to 50	7.5	55	45	16.9
51 to 60	15.6	46.2	53.8	20.7
61 to 70	28.1	53.6	46.4	19.5
71 or older	47.1	50.9	49.1	22.5

Figure 3) Survival of patients with C₁ or D disease. PD Poorly differentiated; WD Well differentiated; MD Moderately differentiated

Figure 4) Survival by age at diagnosis. No significant difference except for patients older than 71 years

15 months compared to 22 months for the rest of the group (significantly different at $P=0.05$).

CONCLUSIONS

A total of 1212 cases of colorectal cancer in the province of Manitoba were reviewed (all cases from 1974 to 1976) with a mean follow-up of nine years. The most important factor in survival was stage of disease. However, it is very significant, especially when interpreting screening studies in the future, that even early disease (A and B stage) had a continued relapse pattern.

Although this is a retrospective study and many patients reported with A or B stage disease may have had more advanced disease because of inaccurate staging, the authors did take care to try to ensure from the records the accuracy of the staging. This pattern of relapse would then be analogous to breast cancer (9). This has not always been seen by others (10-11) and flattening of the survival curves around 10 years may be seen. The death rates from recurrences varied with the different stages.

The most significant factor in survival in colorectal cancer appears to be stage. Some interrelationship exists between stage and differentiation of the tumours as indicated in Table 4. There was a significant difference in survival when comparing stages C₁ and D of the well differentiated and the poorly differentiated groups, indicating the importance of tumour differentiation even expressed crudely in a provincial retrospective study. In fact, 10% of the well differentiated group with stage D at presentation survived over three years without intervening treatment.

The independence of stage and histology was confirmed by multivariate regression analysis. These facts must be borne in mind when comparing surgical resection studies with 'normal survival patterns'. The well differentiated group more frequently presented with isolated metastases and some had a prolonged survival even without surgical intervention. It might be speculated that the well differentiated group is the type of histologic grade represented in surgical resection of metastases. Since a proportion of these individuals will obvious-

ly survive years without surgical intervention to remove metastases, it underlines the need for carefully controlled studies of all such interventions.

The continued relapse pattern seen in early stage disease calls careful attention to screening studies and claims of cure based on the theory of orderly progression. Screening studies should incorporate tumour differentiation to analyze whether the more poorly differentiated groups subsequently show up with metastases.

Sex and age had no effect on survival. The youngest age group could not be adequately examined due to the small

number of patients. Individuals older than 71 years at diagnosis may have a poorer survival, but factors other than cancer may have contributed to these results. Of some interest in this study is the higher than expected incidence of colorectal cancer in the urban areas compared to rural areas. This was still significant, although at a lower level, when the authors attempted to correct for people moving to the city upon retirement and then developing their cancer. Rural or urban cancers were identified by the address of the patient at diagnosis. By reanalyzing data for people under the age of 60 the authors hope to have at

least partially corrected for population movement. Since the greatest incidence of disease is in the older population, it cannot be entirely ruled out that older groups retired and moved to urban areas before their tumours were discovered.

There was apparently no benefit of adjuvant 5-fluorouracil in this retrospective study and the drug may have been detrimental. However, the reasons physicians chose to treat particular patients clearly may have biased the authors sample. Randomized trials have to be done to see the effect of adjuvant therapy but in view of this result, a no treatment control would seem to be an important trial design.

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