Predictors of surgery outcome for colorectal carcinoma in the United Arab Emirates

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عوامل التكهُّن بنتائج جراحات سرطان القولون والمستقيم في الإمارات العربية المتحدة

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خلاصة: في هذه الدراسة الاسترجاعية، تمت متابعة حالات اثنين وسبعين مريضاً بسرطان القولون والمستقيم لمدة متوسطها 28.8 شهراً. وتم تحديد عوامل التكهن بانتكاس الحالة ومدة البقاء على قيد الحياة، وذلك باستعمال التحليلات المعيارية. وأسفر التحليل ذو المتغيِّر الواحد عن وجود فئة من المرضى ينكس المرض فيهم بعد مدة أقصر. وكان المتوسط الإجمالي للبقاء على قيد الحياة 63.2 ± 7.7 شهراً. كما كانت مدة البقاء على قيد الحياة أقصر في المرضى الأصغر سناً الذين أجريت لهم جراحة تلطيفية، وحدثت بهم نقائل بالعقد اللمفية وعقد بالصفاق. وبإجراء تحليل كوكس العديد المتغيرات للمخاطر النسبية، وجد أن نسبة المخاطر للعقد اللمفية الإيجابية تبلغ 2.54 (95% CI: 1.36 – 4.79) مقارنة بالعقد السلبية. وفيما يتعلق بالطورين ألف (A) وباء (B) بالمقارنة بالطور جيم (C) بحسب تصنيف ديوك، فقد كانت النسبة 0.45 (95% CI: 0.25 – 0.81).

ABSTRACT In this retrospective study, 72 patients with colorectal cancer were followed up for a mean period of 28.2 months. Predictors of recurrence and survival were determined using standard analyses. Univariate analyses identified a group of patients with a shorter time to recurrence. The mean overall survival time was 63.2 ± 7.7 months and survival time was shorter for younger patients with palliative resection, lymph node metastasis and peritoneal nodules. In multivariate Cox proportional hazards analysis, the hazard ratio for positive lymph nodes was 2.54 (95% CI: 1.36–4.79) compared to negative nodes, and for Dukes' stages A and B compared to stage C it was 0.45 (95% CI: 0.25–0.81).

Eléments prédictifs de l'issue de la chirurgie du carcinome colorectal aux Emirats arabes unis
RESUME Dans cette étude rétrospective, 72 patients atteints de cancer colorectal ont été suivis pendant une période moyenne de 28,2 mois. Les éléments prédictifs de la récurrence et de la survie étaient déterminés à l'aide des analyses standard. Les analyses univariées ont identifié un groupe de patients ayant un temps de récurrence plus court. La période de survie globale moyenne était de 63,2 ± 7,7 mois et la survie était plus courte pour les jeunes patients ayant une résection palliative, une métastase des ganglions lymphatiques et des nodules péritonéaux. Dans l'analyse multivariée de Cox à risques proportionnels, le taux de risque pour les ganglions lymphatiques positifs était de 2,54 (IC 95 % : 1,36-4,79) par comparaison avec les ganglions négatifs, et pour les stades A et B de Duke par comparaison au stade C, il était de 0,45 (IC 95 % : 0,25-0,81).

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Introduction

Carcinoma of the colon and rectum accounts for over 150 000 deaths annually worldwide [*1*], and studies have shown that colorectal carcinoma is the leading cancer in Western countries. In spite of advances in adjuvant therapy, surgery remains the only effective treatment for colorectal carcinoma [*2*]. Knowledge of the prognostic factors affecting survival is important so as to predict the outcome of the disease and select groups suitable for a particular adjuvant therapy [*3*]. Some of these prognostic factors, such as the extent of penetration of the colorectal wall [*4*] and lymph node status, are well known [*5*]. Other potential factors include colon obstruction, type of surgery [*6*] and histological tumour type and grade [*7*]. Several schemes have attempted to formulate these prognostic factors into a uniform staging system, the most popular being that of Dukes [*7,8*]. Over the past few decades there has been a trend towards a generally more favourable prognosis for women than men [*9*].

The aim of the present study was to analyse factors of importance for survival and recurrence, in order to develop a set of clinicopathological parameters for predicting the prognosis of colorectal carcinoma after surgery.

Methods

The study series consisted of 81 patients with colorectal carcinoma admitted to Al-Ain and Tawam Hospitals, the two teaching hospitals in Al-Ain City, United Arab Emirates (UAE), between 1985 and 1995. There were 55 males and 26 females with a male:female ratio of 2:1. Their ages ranged from 13 years to 85 years with a mean ± standard deviation of 46.5 ± 12.5 years.

Surgical data

The patients' files in the surgery department were reviewed to obtain the following surgical data: tumour subsite, type of operation (whether emergency or elective), type of resection (whether radical or palliative), lymph node involvement, intraperitoneal tumour spread and presence of liver metastases.

Histological data

The clinicopathological parameters studied for prognostic value were age, sex, resection procedure, tumour size, depth of invasion, nodal involvement, differentiation grade and p53 expression.

Immunohistological staining

Using a monoclonal antibody (mAB) against p53 protein, Pab1801 (Oncogene Science Incorporated, Manhasset, New York), we performed avidin-biotin complex immunoperoxidase staining to detect bound p53 mAB [*10*]. After deparaffinization and elimination of endogenous peroxidase activity, p53 mAB was incubated overnight at room temperature. After being washed in phosphate-buffered saline, sections were incubated with biotinylated horse anti-mouse immunoglobulin G antibody and subsequently with avidin-biotin-linked peroxidase. The substrate used for detection of p53 mAB binding was 0.05% 3,3'-diaminobenzidine with 0.01% hydrogen peroxide. Sections were scored as positive if a distinct nuclear immunoreaction for p53 was found in the identifiable tumour cells.

Histological tumour typing and degree of tumour differentiation was carried out according to Jass et al. [*11*]. Staging of the tumour was by Dukes' method [*8*] into stage A (tumour limited to the bowel wall with no lymph node metastasis), stage B

(tumour infiltrating the bowel wall completely with no lymph node metastasis) and stage C (tumour with regional lymph node metastasis irrespective of the degree of bowel wall infiltration).

Surgical margins

These include the proximal and distal margins as well as the radial margins and were assessed according to de Haas-Kock et al. [*12*].

The patients were followed for 6–120 months, with a mean of 28.2 ± 3 months. The dates of death due to cancer, and local or distant recurrence, were recorded. Local recurrence was defined as tumour recurrence within the initial tumour bed, operative field, anastomosis or structures adherent to the primary tumour [*13*]. The survival analysis excluded 8 patients lost to follow up and one patient who died within 30 days of surgery. Thus the follow-up data were available for 72 of the 81 patients.

The Student *t*-test was used to ascertain the significance of differences between mean values of two continuous variables [*14*]. Survival curves were determined by the Kaplan–Meier method, and differences in survival compared by the log rank test. Multivariate analysis by the Cox model of proportional hazard was used to incorporate all the explanatory variables. Forward stepwise procedures and likelihood ratios test were used to select independent variables with the greatest prognostic value.

Results

Operative data

Of the 81 colorectal carcinomas, 28 were located in the right colon (35%), 22 in the left colon (27%) and 31 in the rectum (38%). The operations were elective in 69 patients (85%), while 12 patients (15%) underwent emergency operations. Tumour resection was performed for 72 patients, 56 of which were potentially curative (78%) and the remaining 16 cases palliative (22%). In 48 patients (59%), there was involvement of local lymph nodes. Intraperitoneal metastatic nodules were detected in 19 patients (23%) and liver metastases in 15 (19%).

Histopathological data

Mucoid carcinoma was diagnosed in 8 tumours (10%), and the remaining 73 tumours were classic adenocarcinomas (90%). They were classified as well differentiated, grade 1 in 29 cases; moderately differentiated, grade 2 in 37 cases; and poorly differentiated, grade 3 in 7 cases. The distribution of Dukes' staging of the tumours was as follows: stage A, 5 cases (6%); stage B, 28 cases (35%); and stage C, 48 cases (59%). The proximal or distal surgical margins were involved in 6 of the 72 resected tumours (8%), while the lateral margins were involved in 16 (22%).

Recurrence

The relationship between the time to recurrence and other variables is given in Table 1. This table shows that the mean time to recurrence was significantly shorter for patients aged below 40 years than those aged 40 years or over ($P < 0.05$). It was also shorter for patients treated as an emergency in comparison to those treated electively ($P < 0.001$), and for patients with local lymph node involvement ($P < 0.05$). Neither sex nor tumour subsite affected the recurrence time. Regarding the pathological factors, the recurrence time was significantly shorter for mucoid than non-mucoid carcinomas ($P < 0.001$) and for late Dukes' stages than earlier stages ($P <$

Table 1 **Relationship between mean time to recurrence and clinicopathological findings by univariate analysis**

Variable	Mean ± s (months)	*P*-value
Sex		NS
Male	49.8 ± 20.2	
Female	60.7 ± 25.4	
Age (years)		< 0.05
< 40	27.5 ± 11.8	
> 40	58.9 ± 24.3	
Tumour site		NS
Right colon	62.8 ± 23.1	
Left colon	48.8 ± 22.9	
Rectum	28.9 ± 13.4	
Type of operation		< 0.001
Elective	63.2 ± 27.0	
Emergency	21.2 ±13.1	
Lymph node		< 0.05
Negative	64.6 ±36.5	
Positive	31.3 ± 19.7	
Tumour type		< 0.001
Adenocarcinoma	56.5 ± 29.2	
Mucoid carcinoma	22.8 ± 20.4	
Tumour grade		NS
1	54.8 ± 25.3	
2	54.2 ± 24.0	
Dukes' stage		< 0.01
A+B	69.3 ± 27.2	
C	22.4 ± 12.7	
Proximal and distal margins		< 0.01
Negative	57.1 ± 24.2	
Positive	19.9 ± 12.3	
Lateral margins		< 0.01
Negative	60.5 ± 29.0	
Positive	19.9 ± 12.0	
p53 status		NS
Negative	44.4 ± 22.3	
Positive	55.6 ± 24.2	

s = *standard deviation.*
NS = not significant.

0.01). Cases with positive proximal or distal margins and lateral margins showed a significantly shorter recurrence time than those with negative margins ($P < 0.01$, $P < 0.01$ respectively).

Survival

The mean overall survival time was 63.2 ± 7.7 months. At the end of the follow-up period, 32 patients showed no evidence of disease, 27 had died of cancer and 13 were still living with the disease. Correlation of survival time with the surgical and pathological variables is shown in Table 2. The mean survival time was significantly shorter for patients aged 40 years or under ($P < 0.05$). Patients treated by palliative resection had a highly significant shorter survival than patients who underwent potentially curative surgery ($P < 0.001$). The mean survival time was significantly related to lymph node status, peritoneal spread, liver metastasis and Dukes' staging ($P < 0.001$ for each factor). The mean survival time was also significantly shorter for patients with poorly differentiated tumours than those whose tumours were well differentiated ($P < 0.01$). Although patients with involvement of the proximal, distal and/or lateral surgical margins showed a shorter mean survival time, this was of low significance ($P < 0.01$, $P < 0.05$ respectively). Figures 1 and 2 show the Kaplan–Meier survival curves for lymph node and p53 status respectively. Both predictors were significant as shown by the log rank test ($P < 0.001$ for lymph node positivity and $P < 0.02$ for p53 protein expression). In the Cox proportional hazards analysis, only the presence of lymph nodes and Dukes' staging were significant by the hazard ratios. The hazard ratio for positive lymph nodes was 2.54 (95% CI: 1.36–4.79) compared

Table 2 **Relationship between mean survival time and clinicopathological findings by univariate analysis**

Variable	Mean ± *s* (months)	*P*-value	Variable	Mean ± *s* (months)	*P*-value
Sex		NS	*Liver metastasis*		< 0.001
Male	50.0 ± 19.7		Negative	78.0 ± 23.6	
Female	86.8 ± 28.1		Positive	16.7 ± 9.6	
Age (years)		< 0.05	*Tumour type*		NS
< 40	33.4 ± 11.8		Adenocarcinoma	72.7 ± 23.9	
> 40	70.9 ± 24.3		Mucoid carcinoma	29.4 ± 13.0	
Tumour site		NS	*Tumour grade*		< 0.01
Right colon	87.4 ± 37.8		1	84.5 ± 28.5	
Left colon	51.3 ± 23.3		2	55.9 ± 20.0	
Rectum	39.0 ± 21.7		3	14.7 ±10.5	
Type of operation		NS	*Dukes' stage*		< 0.001
Elective	72.1 ± 28.5		A+B	64.2 ± 28.0	
Emergency	39.8 ±19.9		C	32.3 ± 15.0	
Type of resection		< 0.001	*Proximal and distal margins*		< 0.05
Curative	89.8 ± 29.2		Negative	78.4 ± 30.5	
Palliative	21.7 ± 7.8		Positive	32.7 ± 17.1	
Lymph node		< 0.001	*Lateral margins*		
Negative	95.8 ± 27.8		Negative	80.2 ± 24.0	< 0.01
Positive	33.8 ± 14.9		Positive	29.0 ± 15.7	
Peritoneal nodules		< 0.001	*p53 status*		
Negative	85.4 ± 23.1		Negative	64.9 ± 25.0	< 0.02
Positive	15.7 ± 13.7		Positive	33.3 ± 15.9	

s = *standard deviation.* *NS = not significant.*

to negative nodes, and for Dukes' stages A and B it was 0.45 (95% CI: 0.25–0.81) compared to Stage C.

Discussion

Patients' age and gender

Our results show that younger patients had an earlier recurrence and poorer survival compared to older patients. These data are in agreement with several published studies [*15,16*]. It is possible that young patients with colorectal cancer possess some genetic alterations which may be related to a more aggressive tumour behaviour.

The prognostic importance of sex has been evaluated in a few studies. Fernandez et al. and Chapuis et al. [*9,17*] found a significantly better survival rate in females than males, but this result was not confirmed in our study nor in some others [*15*]. Wiggers et al. reported that neither age nor sex had prognostic significance for survival [*18*].

Tumour site

Although it is widely accepted that the location of rectal cancer has an effect on patient outcome [*10*], the prognostic value of tumour location in the case of colon cancer remains controversial. In one large study, lesions located in the left colon had the most favourable prognosis, whereas those situated in the sigmoid colon and rectum had the worst outcome [*19*]. Another series showed that left-sided lesions had a greater propensity for late recurrence [*20*]. Our study showed that both mean time to recurrence and mean survival time were shorter for rectal cancer than for more proximal cancers.

Type of surgery

The results of our study showed that patients who underwent radical resection had a significantly longer survival compared to those treated by palliative resection (Table 2). This observation is supported by Poeze et al., who urged that radical resection should always be performed if technically feasible [*21*]. We also demonstrated that the mean time to recurrence following emergency colorectal cancer surgery was significantly shorter than after elective surgery. This is in agreement with Anderson et al. who attributed this difference to the fact that emergency patients usually undergo palliative rather than curative resection [*22*].

Histopathology

The production of mucin by colorectal carcinomas is reported to be associated with a high local recurrence rate and short survival [*23*]. Our results concur with this. Umpleby et al. suggested that this association was due to the tendency of mucinous tumours to be associated with a more advanced stage and local fixation than non-

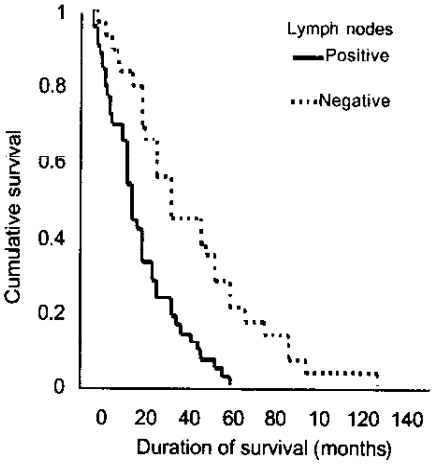

Figure 1 **Kaplan–Meier survival showing the effect of lymph node involvement.**

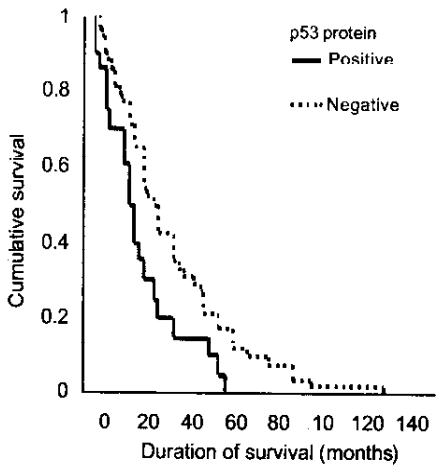

Figure 2 **Kaplan–Meier survival showing the effect of p53 protein involvement.**

mucinous tumours [*23*]. We also found that patients with poorly differentiated tumours had a shorter mean survival time than well-differentiated tumours. These data concur with a previous study [*11*]. The well-established observation that tumour penetration assessed by Dukes' staging has prognostic significance is also supported by our study [*24*]. We observed a frequency of local recurrence of 16%, while the reported frequency in the literature varies between 6% and 50% [*13*]. The variation in local recurrence may be due to unsuspected involvement of the lateral resection margins rather than the proximal or distal margins. This suggestion is supported by our results.

Metastasis

Our study confirmed the well-known prognostic significance of lymph node (Figure 1) and liver metastasis. In addition, we noted that the presence of intraperitoneal tumour spread is significantly associated with shorter survival. This prognostic factor in colorectal carcinoma has been reported in very few studies [*25*]. Our study also confirmed the previously reported deleterious effect of p53 expression on patient survival (Figure 2) [*26*].

Conclusion

To conclude, tumour and surgery-related factors, including patient age, type of surgery (elective or emergency), type of resection (curative or palliative), tumour type (mucoid or non-mucoid), degree of tumour differentiation, stage of tumour infiltration (according to Dukes' classification), resection margin involvement (proximal, distal and lateral margins), lymph node status, liver metastasis, peritoneal spread and expression of p53 protein, can predict the outcome of patients with colorectal cancer. These factors can help to identify patients at higher risk of cancer recurrence and shorter survival for whom adjuvant therapy (chemotherapy and/or radiotherapy) may be helpful.

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