Local recurrence of rectal cancer in patients not receiving neoadjuvant therapy – the importance of resection margins

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(Index words: rectal cancer, local recurrence, linear logistic models)

Abstract

Objectives Local recurrence of rectal cancer reduces quality of life and survival. A multi-factorial linear logistic model was used to analyse risk factors for local recurrence in rectal cancer in patients not receiving pre-operative chemo-radiation.

Methods A case-control study of patients with rectal cancer having surgery with curative intent, between 1996 and 2008. Eighteen putative risk factors for local recurrence were subjected to uni-variate analysis. Significant factors were selected for multi-factorial analysis.

Results Twenty-one patients with local recurrence (cases) and 78 controls were selected. Uni-variate analysis showed significant associations with recurrence for nodal stage (N) (p=0.027), metastasis (M) (p=0.009), adjuvant chemotherapy (p=0.039), positive resection margin (R) (p=0.018) and American Joint Committee for Cancer (AJCC) tumours above stage II (p=0.043). Significant uni-variate odds ratios (OR) were obtained for the same factors. Two linear logistic models were fitted as (1) N, M, R_1 status and adjuvant chemotherapy and (2) AJCC stage, R_1 status and adjuvant chemotherapy. From both models, the only factor significantly associated ($p \leq 0.01$) with local recurrence was found to be a positive resection margin (OR 4.81 and 5.51 respectively).

Conclusions A positive resection margin is the single factor affecting local recurrence of rectal cancer in patients not receiving neo-adjuvant therapy.

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Introduction

Colorectal cancer is the fifth most common cancer in Sri Lanka [1,2]. Most cancers occur in the rectum [3]. Local recurrence following curative surgery is more common in rectal cancer compared to colonic cancer [4]. The potential for cure of locally recurrent rectal cancer is low [5,6]. Aside from surgery-related causes and chemo-radiotherapy, factors suggested to be associated with the recurrence of rectal cancer are tumour location, tumour morphology, and histology and genetic factors [7-12]. Neo-adjuvant chemo-radiation alters many of the histological features of rectal cancer making comparison, even in multifactorial analysis, difficult [13]. Using our rectal cancer database from 1996, we studied factors associated with local recurrence in patients with rectal cancer who had not received neoadjuvant therapy.

Methods

A case-control study evaluated factors associated with local recurrence in those having curative surgery for rectal cancer without pre-operative chemo-radiation. For cases, local recurrence was the inclusion criterion. Exclusion criteria included neoadjuvant chemo-radiation, palliative surgery and atypical histology. In controls, follow up for less than 3 years was an exclusion criterion [14]. Using consecutive sampling and the above criteria, 21 patients with recurrence and 78 controls without recurrence were selected. Based on the literature 18 factors were analysed [10,12]. All specimens were examined after obtaining whole mount transverse sections by one pathologist (JH). A positive margin of resection was defined as that in which tumour-free margin, on light microscopy, was less than 2 mm. Thus, a tumor-free margin was an R_0 resection and a positive margin, an R_1 resection.

Analysis was in two stages. First, each of the 18 factors was tested separately for possible effect on local recurrence. With regard to factors that displayed more than 2 levels (e.g. tumour stage), analysis was also carried out combining some levels. Once putatively significant factors were identified, multifactorial models were fitted. Analysis was by the SAS System V9.00, 2003 (SAS Institute, Cary, North Carolina, USA).

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Results

Median age of patients was 57 years (range 22 to 87). Forty seven (47.5%) were men. Open and laparoscopic, high and low anterior resection, abdomino-perineal resection, restorative procto-colectomy and subtotal colectomy constituted 92% of procedures. Eight types of surgery were defined comprising the above types and other surgery as an eighth.

From uni-variate analysis, node positive tumours (p=0.027) metastasis (p=0.009), adjuvant chemotherapy (p=0.039), positive resection margin (p=0.018) and American Joint Committee for Cancer (AJCC) tumours above stage II (p=0.043), were found to be significantly associated with recurrence using Pearson's Chi-square test (Table 1).

The second stage of analysis was to fit linear logistic models with all the individually significant factors. The AJCC system and the N (nodal) and M (metastasis) stages of the TNM system contained similar information. Two separate models for the two staging systems were fitted and other factors incorporated into both models. Accordingly, one model was with node positivity, metastasis, resection margin and adjuvant chemotherapy (Model 1), the other was with the AJCC stage, resection margin and adjuvant chemotherapy (Model 2, Table 2).

Both models display acceptable deviance and large p values indicating adequate fit of models and no interaction between the factors. In both, a positive resection margin (R1) was identified as the only significant factor with similar odds ratios (4.81 and 3.94). Neither of the staging factors (N, M in the first and AJCC in the second) nor administration of adjuvant chemotherapy appeared significant.

Table 1. **Odds ratio (OR) for factors found significant on uni-variate analysis**

Factor	*OR*	*95% CI*	*p*
Nodal positivity (N+)	3.25	1.16 - 9.10	0.027
Metastasis (M+)	4.29	1.25 - 14.70	0.009
Positive resection margin (R_1)	7.00	2.07 - 23.64	0.018
Adjuvant chemotherapy	2.93	1.03 - 8.36	0.039
AJCC stage III & IV vs. I & II	2.78	1.01 - 7.62	0.043

Table 2. **Odds ratio (OR) calculated using multi-factorial models (1 and 2)**

Model	*Deviance (df)*	*Factors*	*Terms*	*OR*	*95% CI*	*p*
1	65.33; (69)	N status, M status, R_0/R_1 status and adjuvant chemotherapy	Model			0.60
			Nodal positivity (N+)	198	0.52 – 7.63	0.31
			Metastasis (M+)	1.67	0.33 – 8.45	0.54
			Positive resection margin (R_1)	4.81	1.30 – 7.87	0.01
			Adjuvant chemotherapy	1.40	0.37 – 5.33	0.62
2	64.30; (69)	AJCC stage III & IV vs. 1& II , R0/R1 status and adjuvant chemotherapy	Model			0.64
			AJCC stage III & IV vs. 1& II	1.87	0.54 – 6.41	0.33
			Positive resection margin (R_1)	3.94	1.54 – 9.75	<0.01
			Adjuvant chemotherapy	1.47	0.39 – 5.47	0.58

Discussion

This study shows that, if a patient did not receive neoadjuvant therapy, and had local recurrence, a positive resection margin is the most likely cause. This result corresponds broadly to one study where resection margin involvement was the strongest factor predicting recurrence [10]. Associations between recurrence and other histological factors were not observed in our population but have been noted in some European and East Asian studies [10-12].

Univariate analysis indicated 5 factors associated with local recurrence, but multi-factorial analysis showed only one – hence the importance of employing such analysis. The positive association shown between administration of adjuvant chemotherapy and local recurrence in univariate analysis is a case to point. For clinical management, the result supports the importance of neoadjuvant therapy in rectal cancer. However, we have recently shown that pre-operative neoadjuvant therapy should be used selectively; in most with distal rectal cancer and in selected cases of proximal rectal cancer [15]. The limitation in this type of analysis is the need for a control group who may be safely considered free of recurrence. This requires an adequately long period of surveillance – at least three years as in the present study – which, understandably, reduces the number of patients available for study.

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