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Prognostic Factors in Rectal Cancer

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IT HAS been pointed out that there are two outcomes for a patient with rectal cancer: death due to cancer or cure [1]. The patient is cured if the entire cancer is contained within the operative specimen. The extent to which adjuvant therapy can alter the outcome of the non-curative group remains to be determined. Prognosis is, therefore, influenced almost exclusively by the extent of spread of the tumour and the ability of the surgeon to achieve total clearance [2].

Of foremost importance in prognostication will be those features that distinguish between complete and incomplete excision. Incomplete excision can be proven by the demonstration of either distant metastases (preferably with histopathological confirmation) or residual disease within the tumour bed. Incomplete excision can be inferred if the histopathologist demonstrates transection of tumour at a surgical margin, the deep (circumferential) margin being the most important [3, 4]. Incomplete excision is also likely if the tumour has penetrated through the serosal membrane as demonstrated by the presence of tumour cells on the free peritoneal surface (the serosa extends down as far as the mid-point of the mid rectum anteriorly) [4]. Involvement of the apical lymph node (within 1 cm of the level of vessel ligation at the apex of the vascular pedicle) points to the presence of more proximal lymphatic involvement and hence incomplete clearance of lymphatic spread [5]. The preceding features are the most important pointers of an adverse prognosis and their presence or absence should be clearly documented for all patients undergoing surgery for rectal cancer. However, even when these patients are removed as a poor prognosis group, approximately half the remaining patients will eventually die of rectal cancer. [1]. The best explanation for this observation is the presence of occult hepatic metastases at the time of surgery [6].

Prognostication for the apparently cured group is, therefore, an attempt to distinguish between cancers of low and high metastatic potential. It should come as no surprise that the presence of lymph node metastases is the most important prognostic factor for "curative" rectal cancers [1]. A lymph node infiltrated with cancer serves as proof of the acquisition of a metastatic phenotype.

Given that the distinction between lymph node-positive and lymph node-negative rectal cancer is of considerable importance, how much effort should be expended in this exercise? How many lymph nodes should be sampled? How many histological sections should be taken from each node? Should monoclonal antibodies to cytokeratin be used to detect small groups of cancer cells? Should fat clearance procedures be adopted? Should circumscribed nodules of tumour without evidence of residual lymph node tissue be counted as an involved node? The answers to these questions can be found in two papers [4, 5] in which lymph nodes were dissected manually without fat clearance, a single section was taken through each, monoclonal antibodies were not used routinely and tumour deposits without residual nodal tissue were counted as positive nodes. The average number of nodes sampled in C cases was 10 [5]. A clinicopathological staging system was developed as shown in Table 1. By removing 'B' cases with evidence of serosal penetration, incomplete excision or residual disease (to B2, D1, D2), a B1 category was left with the same prognosis as the A3 group [4]. In other words, extension of cancer beyond the bowel wall did not affect prognosis of lymph node-negative cases, providing that patients with proven or likely residual disease were staged appropriately. If positive lymph nodes had been missed, it is likely that the majority would have occurred in cancers extending beyond the muscularis propria (B1 cases). Given the identical prognosis of A3 and B1 cases, the use of extraordinary means to increase the proportion of lymph node positive cases cannot be recommended. Even if such means were recommended, few pathologists would adopt them.

Are there additional prognostic factors for "curative" rectal cancer? It should be pointed out that on the basis of the similar outcome of A3 and B1 cases [4], the only additional need is to stratify C cases. Numerous candidate factors have been proposed including age [5], number of positive nodes [1, 7], apical lymph node status [5], extent of direct spread [1], involvement of the free serosal surface [4, 5], grade of tumour [4, 5], circumscription of tumour margin (expanding or diffusely infiltrating) [1], peritumoural lymphocytic reaction [1], venous invasion [5] and perineural invasion [7]. Which variables are of independent prognostic importance? Multivariate studies published to date fail to provide a complete answer because none has included all the preceding variables in its analysis. Nevertheless, although extent of spread is relatively unimportant in lymph node-negative cases [4], limitation of tumour to the bowel wall is an independent prognostic factor in lymph node-positive cases

Table 1. Australian clinicopathological staging system (ACPS)

Stage	Substage	Spread
A	A1	Mucosa
	A2	Submucosa
	A3	Muscularis propria
B	B1	Beyond muscularis propria
	B2	Free serosal surface invasion
C	C1	Lymph node(s) positive
	C2	Apical lymph node positive
D (incurable)	D1	Tumour transected at excision margin (histological)
	D2	Distant metastases

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(Astler-Coller C1) [5, 8]. It is also certain that number of positive nodes and/or apical nodal status are important and independent factors [1, 5, 7]. There is evidence that "differentiation" is not an independent variable, whereas grading based on the character of the invasive margin (expanding or infiltrating) is [1]. Diffuse infiltration and perineural invasion are closely correlated and only one is likely to be independent (this was diffuse infiltration in an unpublished multivariate analysis by the author). Venous spread is independent in some studies [5] but not others [1, 7]. Age is only relevant when the clinical endpoint is death due to any cause as opposed to death due to cancer [7].

It is clear that the Dukes classification and minor modifications thereof are inadequate for prognostic purposes and for planning adjuvant therapy [1, 5, 7]. Using more refined staging systems (Table 1), a large subset of B cases (B1) can be identified as having the same prognosis as the majority of A cases. There is no rationale for offering adjuvant therapy to patients with ACPS B1 cancers (Table 1). It is likely also that subsets of C cases within favourable prognostic groups do not require adjuvant therapy [1, 7]. Two examples of "good" C cases would be those in which direct spread is limited to the muscularis propria and those associated with a marked peritumoural lymphocyte reaction. There is the proviso that there should not be more than four positive nodes [1], apical lymph node involvement [5], evidence of venous [5], perineural [7] or diffuse infiltration [1], or free serosal surface invasion [5].

If a rectal cancer extends exclusively towards peritonealised rectal wall (a cancer of the upper anterior rectum) and does not extend into the mesorectum, the anatomical factors determining the risk of local recurrence are essentially those of colonic rather than rectal cancer. This should affect the decision to offer adjuvant radiotherapy. Penetration of the peritoneum by tumour is presumably associated with generalised intraperitoneal spread and calls for the development of novel approaches to adjuvant therapy. The importance of the peritoneum in defining the precise location and determining the management of rectal cancer has been neglected [4, 5].

A final issue relates to the range of new technologies that have highlighted potentially important variables such as oncosuppressor gene loss [9] and HLA-DR expression [10]. It is important that such studies adopt a multivariate approach that incorporates a comprehensive set of traditional pathological variables ascertained according to standardised protocols. There is no evidence that any of the new, technology-based variables add to let alone replace the traditional pathological factors.

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The Search for Causes of the Leukaemias

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THE ARTICLE by Groves and colleagues in this issue (pages 941–949) summarises the descriptive epidemiology of these conditions in terms of mortality, incidence and survival. In the last two decades, there have been enormous advances in methods of management so that the prognosis, at least for childhood leukaemia, is now good. It is encouraging to see that this now applies to acute myeloid leukaemia (AML) as well as the dominant childhood leukaemia, acute lymphoblastic leukaemia (ALL). Despite these advances, leukaemia remains a major source of morbidity and mortality in children (around 5% of all deaths in children aged 1–14 years in developed countries and urban areas of developing countries). Although in proportionate terms, the disease becomes less striking in older people, absolute rates are considerably higher in adults than children. There remains a clear challenge to the epidemiologist

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