Pergamon

European Journal of Cancer, Vol. 35, No. 2, pp. 171–172, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(98)00380-3

Editorial

Microsatellite Instability: Impact on Cancer Progression in Proximal and Distal Colorectal Cancers

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ROBERT BENCHLEY noted that people can be divided into two groups: those who divide things into groups and those who do not. Among the 'splitters' of this world, there is a growing conviction that colon cancer can be divided into two groups based on molecular features. In this view, tumours that exhibit microsatellite instability (MIN) tend to occur in the right colon, have diploid DNA, carry characteristic mutations (transforming growth factor β Type II receptor, *BAX*) and behave indolently. Hereditary non-polyposis colorectal cancer (HNPCC) epitomises this route of tumour development. Conversely, tumours with chromosomal instability (CIN) tend to be left-sided, have aneuploid DNA, carry characteristic mutations (*K-ras*, *APC*, *p53*) and behave aggressively. Familial adenomatous polyposis (FAP) epitomises this type of tumour. The designation RER, signifying replication errors, has been criticised because DNA mismatches do not always result from replication errors. MSI has been proposed as a standardised abbreviation, but it lacks the symmetry of MIN/CIN.

Like any broad generalisation, the division of colon cancer into MIN and CIN types probably oversimplifies reality. In this issue, Jernvall and colleagues [1] illustrate one way in which it could be an oversimplification, by suggesting that the prognostic importance of MIN in colon cancer is modified by site. The authors studied 255 patients with colorectal cancer (CRC) from the files of the Finnish Cancer Registry, MIN was discovered in 12% (28/235) of the cases. In accordance with previous descriptions of HNPCC and sporadic tumours with MIN, the MIN-positive group tended to form large, poorly differentiated tumours in the proximal colon. Also in accordance with some previous studies, stage A, B and C MIN-positive cancers of the proximal colon had a 5-year cumulative survival of 100%, compared with 74% in the MIN-negative proximal cancers (difference not significant). Notably, distal MIN-positive cancers fared much worse (21% 5 year survival compared with 52% in the MIN-negative distal cancers). What are we to make of this intriguing observation?

First, we should examine the belief that MIN-positive colon cancers are less aggressive. HNPCC provides indirect evidence for this idea, based on the following line of reasoning: individuals with HNPCC inherit a germline mutation in one of the genes participating in DNA mismatch repair; somatic mutation or inactivation of the wild-type allele results in cells with defective DNA mismatch repair; tumours that develop in this setting almost invariably exhibit MIN; HNPCC has a better prognosis than sporadic colon cancer [2, 3]. There are weaknesses in this argument. First, it cannot be assumed that cancers in clinically defined HNPCC families always demonstrate MIN; in fact, a recent study by Brown and associates [4] found that only 50% of families meeting Amsterdam criteria for HNPCC produced tumours exhibiting MIN. Second, even in MIN-positive HNPCC families the relatively improved prognosis could result from something other than the phenomenon of MIN.

In the sporadic setting, several reports support the idea of improved prognosis for MIN-positive CRC [5–7], but these are anecdotal reports rather than controlled studies. For example, Shibata and colleagues in their seminal paper on MIN [5], described five colon cancers with the phenomenon and noted that 4 of the 5 patients were alive without disease at 4–49 months' follow-up. Subsequent studies have not proven a survival advantage for MIN-positive CRC. Senba and associates [8] compared 17 non-familial colon cancers with MIN with 86 non-familial cancers without instability and found no significant difference in survival. (Senba's figure illustrating cumulative survival rates shows something better than 90% 5-year survival in the MIN-positive group and something less than 80% survival in the MIN-negative group, but the difference was not significant.) The definitive study of this question has not yet been published.

Does left-sided MIN-positive colon cancer behave differently from the right-sided variety? As noted by Jernvall and colleagues [1], the number of cases in their series (six left-sided cancers with MIN) is not sufficient to give the observation statistical significance. We would also like to know more detail about those six cancers, such as:

- What is the DNA ploidy status? In general, tumours with MIN tend to be diploid and those without MIN tend to be aneuploid (thus, the descriptor CIN). But

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Received and accepted 28 Oct. 1998.

overlaps can occur and it may be that some or all of the cancers in question are both MIN-positive and CIN-positive.

- Is there evidence of *p53* mutation? Most MIN-positive colon cancers have normal *p53* function, but Ilyas and associates [9] have demonstrated that left-sided cancers show abnormal p53 expression at about the same rate regardless of MIN status. (The Ilyas study did address the question of survival.)
- What is the histological appearance of the tumours? MIN-positive colon cancers can have distinctive features, among them a solid or solid/cribiform growth pattern, expanding (as opposed to infiltrative) margins, Crohn's-like lymphoid aggregates in tissue adjacent to the tumour and large numbers of tumour-infiltrating lymphocytes (TILs). The last feature, first described by the Mayo Clinic group [10] and recently confirmed by Jass and colleagues [11], seems to be a particularly useful marker of MIN-positive status in sporadic CRC. In our own series, high TIL counts are also a consistent and distinctive feature of HNPCC (data not shown).
- Is there abnormal expression of DNA mismatch repair proteins by immunohistochemistry? Most sporadic MIN-positive colon cancers have inactivation of the *hMLH1* gene due to methylation of the promoter region, This inactivation can be demonstrated immunohistochemically by the absence of MLH1 protein in tumour tissue (and the corresponding presence of gene product in adjacent normal tissue). Such a result in Jernvall's series would support the inference that defective DNA mismatch repair is responsible for the observed MIN.

If the survival difference reported by Jernvall and colleagues persists in larger studies with more thoroughly studied patients, what might it mean? Perhaps (splitters rejoice!) the colon is actually two organs, the right colon and the left colon. Bufill [12] has reviewed the evidence for this view. A striking feature of MIN-positive CRC, whether sporadic or in HNPCC, is the morphological evidence of host immune response in the form of Crohn's-like lymphoid aggregates and TILs. It will be important to see if those morphological markers vary with site and whether such variance indicates differing levels of immune response in the left and right colon.

We believe it is worthwhile to categorise colon cancer as either microsatellite unstable or chromosome unstable (or, conceivably, both or neither). The evidence for differing behaviour is strong enough, we think, that any study purporting to examine prognostic factors in colon cancer must include MIN/CIN status as a variable. It may well prove that further refinements are needed to identify prognostically unique subgroups, such as the MIN-positive, left-sided versus MIN-positive, right-sided distinction made by Jernvall and colleagues.

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