Pergamon

European Journal of Cancer Vol. 31A, Nos. 7/8, pp. 1169–1170, 1995

0959-8049/95 $9.50+0.00

0959-8049(95)00134-4

Grading of Dysplasia

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Lethal carcinomas are still found inadvertently in patients under surveillance; some may not be preceded by conventional dysplasia. However, there is a survival advantage for cancers detected endoscopically rather than symptomatically, and, therefore, by preventing them by colectomy when dysplasia first becomes apparent. It may, therefore, be unnecessary to grade dysplasia when found, for if unequivocally present, then immediate consideration of colectomy is appropriate. It is unreasonable to expect colonoscopists to rebiopsy what might be a minute patch of dysplasia that has no distinguishing features endoscopically. Aneuploidy deserves consideration as a potential marker of patients at particular risk of developing dysplasia, who might undergo more frequent colonoscopy and biopsies than those without the presence of aneuploidy. There is still considerable interobserver variability in the grading of dysplasia by pathologists; part of this may be because grading occurs around a mean, the width of the tails of this distribution curve determining interobserver variation.

Key words: ulcerative colitis, dysplasia, surveillance
Eur J Cancer, Vol. 31A, Nos 7/8, pp. 1169–1170, 1995

THE GRADING of dysplasia by pathologists has become more uniform since the publication of the IBD Dysplasia Morphology Study Group article in 1983 [1]. However, additional information has become available since that time which has raised numerous issues. This includes whether colectomy should be carried out when dysplasia is first detected to keep mortality from carcinoma to a minimum, which in turn suggests that it may be unnecessary to grade dysplasia at all. Let us look at these in more detail.

Deaths from carcinoma in patients under surveillance still occur but the mortality appears to be lower when found at surveillance colonoscopy rather than when presenting symptomatically. Part of the mortality may be the result of continued surveillance rather than colectomy when dysplasia first appears.

In the majority of series reporting the results of surveillance, deaths still occur. There are numerous reasons for this. Major reasons include:

(i) Some patients are followed persistently when dysplasia has appeared; the relatively high rate of associated carcinomas of approximately 30% if high grade dysplasia (HGD) is present and 10% if low grade dysplasia (LGD) is present are data that are only recently becoming available [2]. Once awareness of these data is more widespread, there may be less tendency to follow dysplasia.

(ii) Even in series in which patients are followed very carefully and colectomy carried out when dysplasia is found, occasional lethal carcinomas occur [3].

(iii) In the recent St. Marks' series, it appears that colonoscopy every 2 years is insufficient to prevent Dukes B and C carcinomas [4]. Although the mortality in these patients was zero at the time the paper was submitted, this is to a certain extent fortuitous. Annual colonoscopy, or possibly biennial colonoscopy with flexible sigmoidoscopy, in the intervening years is a possibility but its value remains to be proven.

(iv) Mortality appears to be lower when carcinoma is detected colonoscopically than when it presents symptomatically [4–6].

Dysplasia may be exquisitely focal, and, therefore, difficult to detect. Once found it may be futile to attempt to confirm its presence by re-biopsy. The presence of aneuploidy may be a better indicator of patients at risk of dysplasia and cancer.

Dysplasia may be very focal, and may not be detectable endoscopically using current techniques (see paper by Tytgat and associates, pp. 1174–1177). Such focality in endoscopically unremarkable mucosa militates heavily against its detection in random biopsies. For example, a 2 cm diameter patch of dysplasia (area 3.14 cm^2) would require approximately 32 evenly spaced biopsies in a 100 cm^2 (length 10 cm, circumference 10 cm) segment of bowel to reasonably ensure its detection. In a shortened bowel, 100 cm in length, over 300 biopsies would be required to reasonably guarantee detection! The "logic" of repeating the colonoscopy "to confirm the diagnosis" can be appreciated. Magnification endoscopy and chromoscopy may be able to detect subtle changes not otherwise visible [7]. However, most (but not all) carcinomas and areas of dysplasia appear to develop on the background of an aneuploid mucosa; aneuploidy seeming to precede it [8, 9].

Interobserver variability between pathologists is far from good [10, 11]. This is sometimes used to illustrate potential inadequacies of surveillance. While this is a problem, there are logical explanations for why this should occur. The evolution of dysplasia occurs as a spectrum with a gradual increase in nuclear size, to indefinite for dysplasia, until at some point the cells are considered to be dysplastic, a partially subjective decision. Because, by definition, these are changes similar to those seen in adenomas, and most pathologists see numerous adenomas, this distinction is less of a problem than it theoretically appears. Further, if n pathologists are asked to grade a biopsy, then their

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readings will inevitably form a distribution curve around a mean, the mean of which will be "truth" and the SD of which will be variations between pathologists. If "truth" is exactly LGD, and the tails have 5% of pathologists traversing into indefinite for dysplasia at the low end and 5% traversing into HGD at the high end, then 10% of pathologists will differ by apparently disagreeing about whether a lesion is indefinite or HGD. Further, if "truth" is exactly midway between LGD and HGD, then by definition half of the readings will be of HGD, and the other half of LGD (and possibly even indefinite for dysplasia), so that some degree of disagreement is inevitable, irrespective of the number of pathologists. Finally, readings at either extreme (HGD or negative for dysplasia) can have only one tail, so that disagreement will inevitably be less at both extremes. Other variables include the occasional difficulties in distinguishing marked reactive changes from both HGD and LGD, and problems of interpretation when only a minute portion of the biopsy has HGD in the presence of LGD in the remainder; most (but not all) pathologists tend to shy away from a diagnosis under these circumstances. Nevertheless, these differences are of clinical significance at that part of the spectrum distinguishing the level required for colectomy from that requiring follow-up only, so cannot be trivialised. The surprising finding in the summary of risk by Bernstein, that indefinite for dysplasia carries a similar long-term risk for carcinoma as LGD, suggests that even this distinction may be clinically untenable [2], although the explanation may be that it is already aneuploid and, therefore, at increased risk of carcinoma.

A small number of carcinomas may not be preceded by classical dysplasia; these may be difficult to detect endoscopically and may be advanced when found. Although in some series, dysplasia is found adjacent to all carcinomas [12], this is not always the case [13]. The usual reason invoked is that the tumour has destroyed evidence of its origin. However, other alternatives require consideration. These include the fact that, in the stomach, the diffuse form of gastric cancer has a morphologically very poorly defined pre-invasive lesion which does not resemble the classical dysplasia found in intestinal cancer [14]. Yet, in the stomach these diffuse types of cancer include poorly differentiated and signet ring variants, morphologically similar to those seen in ulcerative colitis (UC). It is, therefore, possible that an analogous pathway exists in the large bowel in UC. Further, endocrine carcinomas are also well documented in UC, and similarly have a very poorly defined pre-invasive lesion; indeed even in related carcinoid tumours, a pre-invasive component is virtually undefined, yet clearly epithelial in origin.

CONCLUSION

The evidence suggests that the philosophy of surveillance should be that while patients are dysplasia-free, the chance of them developing a lethal carcinoma is small, but not zero. Once dysplasia is found, provided the diagnosis is not in question, colectomy is appropriate. Surveillance should probably be carried out annually but particularly after 20 years of disease as the risk increases. A combination of histology and flow cytometry for aneuploidy may provide the best indication that a specific patient is at increased risk of carcinoma.

1. Riddell RH, Goldman H, Ransohoff DF, *et al.* Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Path* 1983, **14**, 931–968.
2. Bernstein CB, Shanahan F, Weinstein WF. Are we telling our patients the truth about dysplasia surveillance in ulcerative colitis? *Lancet* 1994, **343**, 71–74.
3. Lofberg R, Lindquist K, Veress B, Tribukait B. Highly malignant carcinoma in chronic ulcerative colitis without preceding dysplasia or DNA aneuploidy. *Dis Colon Rectum* 1992, **35**, 82–86.
4. Connell WR, Lennard-Jones JE, Williams CB, Talbot IC, Price AB, Wilkinson KH. Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. *Gastroenterology* 1994, **107**, 934–944.
5. Choi PM, Nugent FW, Schoetz DJ, Silverman ML, Haggitt RC. Colonoscopic surveillance reduces mortality from colorectal cancers in ulcerative colitis. *Gastroenterology* 1993, **105**, 418–424.
6. Jones HW, Grogono J, Hoare AM. Surveillance in ulcerative colitis: burdens and benefits. *Gut* 1988, **29**, 325–331.
7. Nagasako K, Fujimori K. *International Symposium on Recent Advances in Inflammatory Bowel Disease.* Nara Japan, November 1994, 1, 2, 5.
8. Lofberg R, Brostrom O, Karlen P, Ost A, Tribukait B. DNA aneuploidy in ulcerative colitis: reproducibility, topographic distribution, and relation to dysplasia. *Gastroenterology* 1992, **102**, 1149–1154.
9. Rubin CE, Haggitt RC, Burmer GC, *et al.* DNA aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. *Gastroenterology* 1992, **103**, 1611–1620.
10. Melville DM, Jass JR, Morson BC, *et al.* Observer study on the grading of dysplasia in ulcerative colitis; comparison with clinical outcome. *Hum Path* 1990, **20**, 1008–1014.
11. Dixon MF, Brown IJ, Gilmour HM, *et al.* Observer variations in the assessment of dysplasia in ulcerative colitis. *Histopathology* 1988, **13**, 385–397.
12. Ransohoff DF, Riddell RH, Levin B. Ulcerative colitis and colitic cancer. Problems in assessing the diagnostic usefulness of mucosal dysplasia. *Dis Colon Rectum* 1985, **28**, 383–388.
13. Taylor BA, Pemberton JH, Carpenter HA, *et al.* Dysplasia in chronic ulcerative colitis: implications for colonoscopic surveillance. *Dis Colon Rectum* 1992, **35**, 950–956.
14. Ghandur-Mnaymneh L, Paz J, Roldan E, Cassidy J. Dysplasia in nonmetaplastic gastric mucosa. A proposal for its classification and its possible relationship to diffuse type gastric carcinoma. *Am J Surg Path* 1988, **12**, 96–114.