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Anastomotic recurrence of colorectal cancer – a biological phenomenon or an avoidable calamity?

Local recurrence after radial surgical excision of a large bowel neoplasm is nothing short of a catastrophe, because it heralds the onset of a progressive, painful, debilitating condition which untreated, has an average survival time of 11 months.[1] As many patients do not have disseminated disease, death is often slow and attended by considerable morbidity.[2] Most local recurrences occur after resection of a carcinoma in the rectum or sigmoid colon.[3] Perineal pain, tenesmus, diarrhoea, incontinence and eventually obstruction supervene.

Once an anastomotic recurrence is diagnosed, treatment is palliative in most patients and options are limited. Surgery offers the only realistic chance of cure, but is rarely feasible. Radiotherapy relieves symptoms in half the patients without altering mean survival.[1] Palliation of obstruction by constructing a stoma, or of urinary obstruction by long term catheterisation[4] causes further distress in an already limited life of poor quality.

The cause of this distressing complication of either restorative resection, or rectal amputation is the subject of considerable debate. The wide variation in the reported incidence of anastomotic recurrence[5-15] may reflect differing surgical techniques, and in particular inadequate local excision of the tumour or its adjacent lymphatics, and inappropriate choice of low restorative resection. Supporters of the theory of exfoliated cell implantation would argue that omission to wash out the bowel ends intraoperatively with a cytocidal agent is associated with a high incidence of local luminal recurrence.[16 17]

Some of these dogmatic surgical views have been seriously questioned in the last decade and there is increasing evidence that there may be a more widespread biological abnormality in a vicinity of the tumour, predisposing some patients to a high risk of local recurrence.

Inadequate excision

Adequacy of local tumour clearance is fundamental to the prevention of locally recurrent disease, but emphasis has previously been placed on the importance of adequate distal clearance, particularly of rectal cancer. There is now substantial evidence that a 5cm distal clearance margin is unnecessary and that submucosal infiltration, lymphatic metastases and islands of tumour tissue are rarely present more than 2cm away from the macroscopic edge of the growth.[18 19] Furthermore, although some authorities have implied higher local recurrence rates after restorative resection, particularly with the widespread use of stapling devices and a decreasing frequency of abdominoperineal excision, there is not a shred of evidence that sphincter saving surgery is accompanied by a higher rate of local recurrence.[20-25]

Adequate excision of the mesorectum is probably more important. The

presence of micrometastases in the mesorectum was highlighted by Heald and others in 1982[26] and a recent review of his own 2·6% incidence of local recurrence supports the view that wide excision of the mesorectum is probably a most important factor in achieving these commendable results.[27]

In our view inadequate lateral clearance has received insufficient recognition. Durdey and colleagues found that 38% of patients had microscopic involvement of the lateral margins of the resected specimen. After a median follow up of 23 months, 75% of those with microscopic evidence of lateral spread had developed a local pelvic recurrence.[28] We have found that cytological smears from the four quandrants of the pelvis and imprint cytology of the tumour bed are a reliable indicator of inadequate tumour clearance. Of 60 patients studied, 12 had positive malignant cytology, and after a mean follow up of 16·5 months (range 1–38 months), seven of those developed a local recurrence (personal communication). We feel that cytology can identify patients with a high probability of local recurrence, in whom early postoperative radiotherapy may be advisable.

Implantation of exfoliated malignant cells

A further contentious cause of local recurrence is the possible implantation of exfoliated malignant cells into the anastomosis.[30-32] Large bowel cancer may recur as nodules in the abdominal or perineal wound, as well as at the colonic anastomosis, suggesting that the mechanism of implantation of viable tumour cells might be an important cause of recurrence.[33,34] Some but not all centres,[35,36] have shown exfoliated tumour cells to be capable of excluding vital dyes such as trypan blue[37] and fluoroscein.[38] Exclusion of vital dyes and fluorescein however, does not mean that the cells are capable of active division to produce new tumours *in vivo*. Malignant cells harvested from the lumen of the bowel are capable of growth in cell culture, but the cultures are self limiting and regress at seven to 10 days.[39]

The only convincing test for replication is the ability of exfoliated malignant cells to produce tumours in immuno deprived mice. Only one study has claimed that injected suspensions of malignant cells into the tail vein of immuno deprived mice produced metastases, and even then the tumours did not display the histological pattern of the parent colorectal neoplasm.[40]

In vitro studies have shown that certain solutions, particularly chlorhexidine-cetrimide and povidone-iodine rapidly kill exfoliated malignant cells, again using exclusion of vital dyes as the criterion of viability (personal communication).[41] Hypochlorite solution, or mercuric perchloride have been traditionally advised for operative washout before fashioning intestinal anastomoses after tumour resection,[43] but this has never been tested scientifically. Until the results of a randomised clinical trial comparing peroperative cytocidal washout with a placebo washout are available, clinicians will never know whether this time honoured practice is justified.

Altered biological properties at large bowel anastomoses

An alternative and largely unexplored mechanism for local recurrence is the possibility of some biological change at the anastomotic site, which increases

the susceptibility to cancer. Animal studies have consistently shown an increased yield of bowel tumours at the site of transection, stoma formation, anastomosis after resection, or merely the placement of a non-absorbable suture,[44] irrespective of whether the insult occurs before or after administration of one of the common chemical carcinogens, such as DMA, DMH, azoxymethane and MNNG*.[45-53] A paper in this issue of *Gut* provides further evidence of proliferative instability in close proximity to a colonic anastomosis.[54]

Using the azoxymethane rat model, Roe and colleagues from Bristol have reaffirmed an increased yield of tumours at the site of a surgical insult. They have shown that tumours occur irrespective of the timing of the carcinogen in relation to the operation and within a maximum time studied: three months. It is interesting that the greatest number of tumours were found when the carcinogen was given immediately postoperatively, whether in the sham, or in the transection group. Perhaps their hypothesis of immediate postoperative hyperaemia carrying high concentration of the carcinogen to the anastomosis is responsible in the transected animals, but it is not applicable to the controls. By measuring crypt cell height and mitotic index they have shown disordered cell kinetics in the 10 crypts adjacent to the anastomosis, even when histological evidence of re-epithelialisation of the anastomosis was complete. The crypt cell height had in fact returned to normal at 12 weeks and the labelling index was tending to fall. It would have been interesting to prolong the experiment and see when this variable also returned to normal. The fact that the tumour yield in the animals having the carcinogen 12 weeks after surgery was still highest at the site of the anastomosis must indicate, however, a continuing susceptibility to malignant change. The techniques used in the study do not account for cell cycle time, nor provide dynamic assessment of the birth rate of crypt cells. Technically more difficult stathmokinetic methods are better estimators of cellular proliferation. We believe these methods should be applied to examine the correlation between hyperplasia and neoplasia.

Matthews, Cooke and coworkers[55] have done a preliminary study of this kind with a few animals and highlighted some of the difficulties of the method. Their early data support the view that there is a close association between reparative hyperplasia and neoplasia, perhaps because of the selective action of chemical carcinogens on the stem cells.[16 17]

Other reports suggest that there are altered biological properties in the mucosa adjacent to a large bowel neoplasm. Sulphomucin staining of colonic mucosal goblet cells is associated with increased cell kinetics and is common adjacent to a large bowel tumour.[56 57] Sulphomucin staining at the site of an anastomosis is associated with an increased risk of local recurrence after apparently curative resection.[58 59] Flow cytometric analysis has also shown that aneuploid tumours not only carry a poor prognosis, but are associated with increased risk of local recurrence.[60-62]

Finally, we must ask the question: are the tumours at anastomoses in the animal model the same as those in man? We think not. The true mucosal intraluminal anastomotic recurrence is not common. Large bowel cancer is often associated with polyps adjacent to a tumour and also present elsewhere in the colon.[43] In some cases local recurrence may be because of malignant change in a residual adenoma. Some apparently 'local'

* DMA–2,3-dimethyl-4-aminobiphenyl; DMH–1,2-dimethylhydrazine; MNNG–N-methyl-N-nitro-N-nitrosoguanidine.

recurrences are missed synchronous tumours,[9] whilst late recurrences may arise from a metachronous tumour developing close to the anastomosis. In most patients local recurrence is largely extrarectal and the lesion seen and biopsied through the endoscope is merely the tip of the iceberg. In our view, the term 'anastomotic recurrence' is misleading. These recurrences rarely appear to be mucosal, but are mostly pelvic, suggesting that mechanisms other than local intraumural reparative processes are important in their pathogenesis.

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