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### A pathological study of tumour regression in oesophageal adenocarcinoma treated with preoperative chemoradiotherapy

We read with interest the study of adenocarcinomas treated by preoperative chemoradiotherapy by Dunne *et al.*<sup>1</sup> This broadly paralleled our study into the subject of adjuvant treatment before surgery for oesophageal carcinoma. These results have been published in abstract form previously,<sup>2</sup> and may be summarised as follows.

We studied a series of 29 patients (23 men, six women; average age, 59 years for men, 62 years for women) over a period of three years (1998 to 2000), who had confirmed oesophageal carcinoma (adenocarcinoma, squamous carcinoma) and were treated with radiotherapy (30 in 10 fractions or 45 Gy in 25 fractions) and chemotherapy of cisplatin (80 mg/m<sup>2</sup>) and 5 fluorouracil (1 gm/m<sup>2</sup>) in weekly cycles for four weeks. Four patients did not undergo resection; three showing disseminated disease and one dying of gastrointestinal haemorrhage before surgery. The remaining nine patients with squamous carcinoma and 16 patients with adenocarcinoma underwent resection of the tumours with local node sampling.

Five of the patients with squamous carcinoma and five with adenocarcinoma showed no viable tumour after preoperative adjuvant treatment. In a manner similar to the above study, we found standard features of radiotherapy in the form of fibrosis, vascular changes, radiation fibroblasts, and occasional zones of necrosis containing amorphous matter. We determined the pretreatment level of tumour spread by means of identifying either degenerate keratin (derived from the squamous carcinomas) or mucin pools (in cases of adenocarcinoma). Residual viable tumour could be staged in the normal fashion, depending on whether one used TRG or TNM methods. We would emphasise the usefulness of a mucin stain to determine pools of mucin within lymphatic channels

and/or lymph nodes as a method of highlighting the extent of adenocarcinoma spread, but would also advocate the need for a cytokeratin or equivalent stain to identify single residual tumour cells. This parallels the concept of "skip metastases" described by Hosch *et al.*<sup>3</sup>

All of the tumours studied were completely excised at the peripheral plane of resection, but seven cases revealed metastatic nodal disease (one squamous, six adenocarcinoma). In several of these cases the metastatic tumour was determined as being outside the field of radiotherapy. At the time of the last analysis, 18 of these 25 patients were alive with follow up periods ranging between four and 30 months. Overall, we concur that these studies, and others,<sup>4</sup> appear to indicate a survival advantage in the arena of oesophageal carcinoma treatment.

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### Paradoxical severe decrease in serum HDL-cholesterol after treatment with a fibrate

Crook *et al* recently reported a paradoxical decrease in serum high density lipoprotein-cholesterol (HDL-C) in a patient who was receiving fibrate (bezafibrate) treatment for hyperlipidaemia.<sup>1</sup> Reviewing the literature, they rightly highlighted some of the characteristics that have so far been observed in association with this phenomenon, namely: (1) it occurs with fibrate monotherapy, in addition to when fibrates have been combined with other hypolipidaemic agents; (2) it appears to be a class effect of the fibric acid derivative group of drugs, having been seen with all the major fibrates; (3) there may sometimes be a fibrate dose dependency; (4) it may not be consistently reproducible if affected patients are re-challenged with a fibrate; and (5) there is an increased catabolism and decreased synthesis of apolipoprotein A containing lipoproteins. However, they fail to mention important observations from another report involving ciprofibrate monotherapy,<sup>2</sup> which suggested that a severe reduction in serum HDL-C may become evident as early as two weeks after initiating treatment, that HDL-C concentrations varied widely during the course of treatment, and

that full recovery of HDL-C may be observed from two weeks after cessation of the offending fibrate.

The fibrates, effective as lipid lowering agents and ameliorators of the "atherogenic profile", are an important tool in cardiovascular risk management and are widely used for this purpose. In fact, the recognised effect of fibrates on HDL-C is an increase in serum concentrations of the lipoprotein. The reason(s) why some individuals are susceptible to reductions in serum HDL-C when receiving treatment with fibrates are unclear, and the mechanism(s) underlying the phenomenon remain speculative. Likewise, the clinical implications have not been considered; but an iatrogenic very low serum HDL-C concentration is unlikely to be beneficial because HDL-C is believed to be cardioprotective. In this context, there is no indication from most of the published cases, including the one by Crook *et al*, that patients have complained of symptoms temporally related to low serum HDL-C in the short to medium term. Indeed, there is only one report in which an affected patient was judged to be symptomatic (dry mouth and tiredness); these symptoms improved when the fibrate was stopped.<sup>3</sup> Apart from the dozen or so cases of fibrate induced reductions in serum HDL-C that have been formally reported in the literature, there is anecdotal evidence that many more patients may be affected. It is unknown just how large this population is.

These are important questions requiring evidence based answers. Such answers can be provided only by systematic investigation of affected patients, preferably via a nationwide study coordinated centrally by an expert group. All the necessary technological and clinical tools are available and the molecular basis of the action of fibrates is now known in some detail.<sup>4,5</sup> The resolution of this clinical conundrum will enhance knowledge, demystify fibrate related hypoalphalipoproteinaemia, and reassure both clinicians and patients.

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## Conversion to core biopsy in preoperative diagnosis of breast lesions: is it justified by results?

Shannon and colleagues<sup>1</sup> conclude that conversion to core biopsy increases sensitivity and specificity and reduces the inadequate rate, and advocate the abandonment of fine needle aspiration (FNA) in the preoperative diagnosis of breast disease.

In their experience, the inadequate rate for FNA in the symptomatic breast disease context of 35% is certainly untenable, but it would be appropriate to evaluate the application of the technique rather than the technique itself. The authors provide no data on the structure of their FNA service: were the aspirates performed by a limited number of trained and experienced aspirators? What indications were considered appropriate for FNA? Was there rapid assessment of FNA with repeat of inadequate samples?

An additional factor may be the technique used: 21 gauge needles are very large bore for symptomatic breast FNA, and better results can be obtained with smaller gauge needles (23 gauge),<sup>2</sup> whereby discomfort is reduced, blood contamination is reduced, and cell yield is satisfactory.

The structure of a service where the inadequate rate of FNA is as high as 35% must be seriously questioned. In our experience in symptomatic breast disease practice, the use of FNA within a triple assessment context complemented by core biopsy in situations of significant discordance between modalities is a robust and accurate diagnostic modality.

By limiting the technique to a small number of skilled aspirators (in our case two cytopathologists) and incorporating rapid microscopic evaluation of adequacy at a triple assessment clinic, the inadequate rate is low (< 15%) and other performance criteria are acceptable (complete sensitivity, 88%; full specificity, 80%; false negative rate, 5%; false positive rate, 0%; parameters calculated using methodology detailed in National Health Service breast screening programme guidelines for cytology). The addition of core biopsy in situations where triple assessment is discordant allows accurate preoperative diagnosis in virtually all cases.

Absolute and complete sensitivity with FNA will never match that of core biopsy, but that is not always the point: most patients attending symptomatic breast disease clinics do not have malignant disease, and a benign diagnosis on triple assessment including FNA allows a definitive diagnosis to be made at a single outpatient visit, alleviates patient anxiety, and offers considerable cost effectiveness in terms of outpatient clinic time and resources. The requirement for core biopsy is reduced by the use of FNA, particularly in the context of benign disease. Clear protocols for further investigation of situations of discordant triple assessment (including core biopsy) safeguard against false negative diagnosis and missed cancer.

Core biopsy is certainly a robust and reliable diagnostic modality, but it has some important disadvantages in terms of delay in diagnosis and patient discomfort (I would dispute that core biopsy is less traumatic than FNA<sup>1</sup> when FNA is performed using a 23 gauge needle).

When used in the appropriate setting FNA has an important role in preoperative diagnosis of symptomatic breast disease and should not be abandoned without due consideration

to its appropriate use and the structure of the service within which it is applied.

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## The use of a standard proforma in breast cancer reporting

According to a recent paper in this journal by Mathers *et al.*,<sup>1</sup> the use of a standard proforma for breast cancer resulted in 74% completeness of reporting. However, there is no mention in that paper, or in other reports of audits of compliance with standard data sets,<sup>2–5</sup> of clinicians requesting missing data, or of the issue of supplementary reports.

At the Royal London Hospital, we recently audited colorectal cancer resection histopathology reports for compliance with the Royal College of Pathologists' Minimum Data set (MDS). At the ensuing audit meeting, various reasons for non-compliance with the MDS were discussed. It was obvious that not all data items in the MDS were appropriate for every case and that it might be unrealistic to strive for full compliance with the MDS. Indeed, clinicians may have ignored omissions not relevant to patient management. Relevant missing data may have been provided verbally at multidisciplinary team meetings, but few written supplementary reports were issued.

If an MDS truly is minimum, then published reports of audits and our audit have shown that large proportions of patients have their management planned without essential pathological data. Full compliance can probably only be achieved by rigid adherence to the MDS, and by issuing supplementary reports if data items are missing. Unfortunately, full compliance is probably necessary, even when data items are of no clinical relevance, so that accusations of failure to comply with a "minimum" standard are avoided.

To cover every angle, perhaps histopathology cancer audits should record not only compliance with the MDS, but also whether the report was optimal for planning patient management, whether the multidisciplinary team meeting requested further information, and whether supplementary reports were issued.

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## Authors' reply

We are grateful to Dr Jeffers for his response. Our paper<sup>1</sup> and his letter raise important issues regarding the future viability of a cytology led service for the preoperative assessment of breast disease. In our centre, fine needle aspiration cytology (FNAC) and core biopsies were performed in the main by either consultant radiologists with a specialist interest in breast disease (where radiological assistance is required) or specialist breast surgeons. The investigations were not performed within the setting of a single attendance ("one stop") clinic.

We accept that FNAC supplemented by core biopsy in a rapid diagnosis setting may be considered by clinicians and patients alike to be a satisfactory service, but we would argue that this is the only potential benefit FNAC has to offer. To be a viable proposition this requires the regular availability of an experienced cytopathologist seeing many aspirates on a regular basis, together with appropriate cross cover for annual leave/sickness. Dr Jeffers indicates that this is so in his department, but we suggest that this may not be the case in many centres and would be costly to set up.

The single attendance (one stop) clinic can be advertised as an attractive and a popular innovation, but in this climate of evidence based medicine the demonstration of advantages in patient management and cost benefit analysis are required.<sup>2</sup> A recently published analysis of one stop breast clinics directly dealing with these issues has shown a reduction in patient anxiety (which was only detectable over the first 24 hours but not at three weeks or three months).<sup>3</sup> For the first time, this study analysed costs and showed that savings from the reduction of frequency of outpatient visits were more than offset by the increased costs associated with same day diagnosis (£32 for each patient). The authors conclude that this additional cost to the National Health Service may not be justified by the short term reduction in anxiety.

Dr Jeffers argues for a role for FNAC in benign breast disease to provide immediate reassurance. Perhaps it is time to consider whether simply calling a lesion benign or malignant (neither of which constitutes a diagnosis) is enough. We would argue that core biopsies are more likely to provide a definite benign diagnosis. We show reduced suspicious rates rather than having to accept C1 as an absence of malignant cells and to struggle with the cases given a C3 diagnosis, which would probably proceed to core biopsy any way. Surgical colleagues have shown that automated core biopsy has a superior diagnostic power compared with FNAC in breast cancer diagnosis.<sup>4</sup>

Other arguments for favouring core biopsy over FNAC for palpable lesions are well rehearsed (assessment of invasion, tumour type, grade, and oestrogen receptor status are more amenable by the former). Mammographically detected lesions in the context of screening require a different approach because there are radiological abnormalities that require pathological explanation (such as microcalcification, distortion, asymmetric density, etc) and that often cannot be investigated satisfactorily by means of FNAC. In addition, we suggest that core biopsies are more readily and accurately

interpreted by pathologists who are considered "non-specialist" compared with needle aspirates, resulting in less reliance on the presence of a small group of individuals for a clinic to run smoothly, and fewer difficulties in the provision of cover for staff absence.

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## ECHO



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### Molecular diagnosis may help management of ocular infection

Thousands of people worldwide may benefit from a promising new method to confirm an infection that is a leading cause of blindness. Preliminary indications from a study between India and the United States are that PCR might be used to diagnose fungal keratitis of the cornea, which commonly affects agricultural workers in developing countries.

Results with PCR and conventional methods showed complete matching in most patients with suspected infection who were tested (22/30, 74%). Three samples (10%) were PCR positive, culture negative, but in two the patients were judged clinically to have fungal infection. Conjunctival swabs from the healthy eye in each patient were PCR negative, culture negative in all but five patients (17%), whose infected eye was positive for fungal infection.

PCR was very sensitive—down to minimal amounts of fungal material. Specificity tests showed cross reactivity with several filamentous fungi, but not with *S cerevisiae*, nor with a range of bacteria.

The researchers obtained scrapings from patients in India with presumed fungal keratitis of the cornea and a conjunctival swab from the other eye. The samples were treated with two rounds of amplification of part of the fungal 18S ribosome sequence. The first was of a segment common to *Candida albicans*, *Fusarium oxysporum*, and *Aspergillus fumigatus*. The second was nested amplification with three different primer pairs for variable sequences for each species. Sensitivity and specificity were determined against human fungal pathogens, including *Candida*, *Aspergillus*, other species of fungi imperfecti, *Cryptococcus*, *S cerevisiae*, and reference strains of a range of bacteria.

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## Paradoxical severe decrease in serum HDL-cholesterol after treatment with a fibrate

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