diagnosis of BSE, and so on, was clearly crucial in ensuring the credibility of the results.

Regrettable as it is to question the results from an organisation as eminent as the IAH, the effect of these kinds of research studies on blood-safety policy demands that there is maximum confidence in the quality of the laboratory practices of the institutions involved.

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Preoperative and postoperative radiotherapy and survival in colorectal cancer

Sir—The Colorectal Cancer Collaborative Group (Oct 20, p 1291)[1] report a systematic overview of adjuvant radiotherapy for colorectal cancer that replicates previous findings on the administration of this treatment for resectable rectal cancer.[2] They conclude that preoperative radiotherapy significantly reduces 5-year cancer-related mortality and local recurrence compared with surgery alone.

They report that the 5-year overall mortality was only marginally better in patients who were assigned preoperative radiotherapy than in those assigned surgery, despite the impressive reduction in the annual risk of death from rectal cancer (12·9%) by preoperative radiotherapy. We have some questions about the statistical analysis and interpretation of results.

The Collaborative Group state that, although crude mortality data could be extracted from three randomised controlled trials (RCTs), they were not included in the overview because quality assessment was impossible. Which method did they use for scoring the quality of the RCTs included in the meta-analysis? Why were they unable to assess the quality of the RCTs excluded? Generally, a trial should not be assumed of quality not good enough to be included in a meta-analysis just because the quality assessment was not possible.

Also perplexing is why the Essen RCT (reference 8 in the report), which combines preoperative and postoperative radiotherapy, was included in the meta-analysis. The Collaborative Group report the same (30%) overall mortality rate in the two groups after a median follow-up of 58 months, whereas in the meta-analysis a benefit on survival was reported in the control group. Why was the Japanese study (their reference 21), in which chemotherapy was administered postoperatively in both groups, included in the meta-analysis? In the MRC I trial (their reference 3), two different treatment groups were compared with the same surgery groups as control. Any analysis that uses two comparisons from the same study needs to adjust for correlations that arise in two comparisons because the units are not independent. All of the analyses in the paper in which the number of comparisons exceeds the number of trials are, therefore, incorrect.[3]

The subgroup analyses of the effect of preoperative radiotherapy at a biologically effective dose of 30 Gy or more on overall mortality by age (2952 patients) and Dukes' stage (2894) in patients who have been curatively resected, is based on fewer than half of the total patients included in the main analysis of overall mortality. Whatever the outcome, this analysis should be interpreted extremely cautiously. The conclusion that the treatment benefit is a function of these factors is not well supported, since more than half of the patients cannot be included in the analysis (a potential bias that is unexplored).

The researchers could look to do a regression analysis on the total patients included in the main analysis including tests of interaction to see if age and Dukes' stage modify the effect of treatment.

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Sir—The Colorectal Cancer Collaborative Group[1] clearly show that neither preoperative nor postoperative radiation therapy has an appreciable effect on overall survival in patients with this disease.

Patients who received postoperative radiation therapy did have a 9% lower risk of death from rectal cancer than controls. But this survival advantage was all but wiped out by the more frequent deaths from other causes in the radiation therapy group. Overall, the risk of death from causes other than rectal cancer was 15% higher in those who received radiation therapy than in those who did not, a significant difference.

The Collaborative Group state that there was no clear benefit of radiotherapy for overall survival. Yet, B Minsky, in his Oct 20 commentary,[2] believes that the study results support the use of adjuvant radiation therapy for rectal cancer. That conclusion arises because preoperative radiation therapy did decrease the chance of a recurrence at 5 years by 7%. The Collaborative Group also believe that since uncontrolled local recurrence can have a devastating effect on patients' quality of life, improved local control with radiotherapy might be a sufficient benefit to justify this treatment's use.

Yes, uncontrolled local recurrences are devastating. But so too are excess deaths caused by radiation therapy, such as through cardiovascular disease, infections, and other, unknown, causes. The researchers and Minsky do not mention that the side-effects to the bowel of radiation therapy can devastate patients' quality of life. Patients receiving radiation therapy for rectal cancer have more chronic bowel dysfunction than do those who undergo surgical resection alone.[3] Diarrhoea, bleeding, tenesmus, and pain on defecation are frequent during therapy.

These symptoms commonly subside when treatment stops. However, 6 months to 1 year or more later, delayed postradiation symptoms can develop. In one textbook these symptoms are described: "There may be two to four or even eight or more

bowel movements a day, and the urgency may be compelling. Blood is also often seen. Tenesmus is frequent, and cramping pain is often associated with defecation. Radiation proctitis frequently is associated with pain and bleeding; the latter may be severe and persistent, occasionally requiring transfusions . . . Severe or complete obstruction may develop."[4]

Any assessment of radiation therapy must take into account not just the statistical effect of treatment on recurrences, but what patients actually experience as a result of the treatment. What patients and their families need is the complete picture, of costs as well as benefits, without which it is impossible for them to make educated treatment decisions. But how many rectal cancer patients, I wonder, are told that adjuvant radiation therapy has not been proven to extend life but may in fact cause serious short-term and long-term adverse effects? How many are told that adjuvant radiation may in fact lead to their untimely deaths?

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Authors' reply

Sir—In response to Calogero Cammá and colleagues, we were unable to confirm that the three excluded studies were properly randomised by checking individual patients' data or by contact with the investigators. Moreover, the exact matching of the number of men and women, and of older and younger patients in each group in the São Paulo study (in which an unusually large benefit was reported for radiotherapy) suggested that matched rather than randomised controls may have been used, which would have made this trial ineligible. Given the small size of the omitted studies, however, their inclusion or exclusion makes no material difference to the findings—the reduction in the yearly odds of death is 5·7% (SE 2·6) with, and 5·4% (2·9) without these studies.

As we described, we included the Essen and Japanese studies as unconfounded trials of preoperative radiotherapy. We report a non-significant trend towards benefit for controls in the Essen study, which is consistent with the published findings. Separation of the MRCI 5 Gy and 20 Gy comparisons in figures 1, 5, 6, and 7 (but not figures 2, 3, or 4) makes no difference; for example, the reduction in the odds of death in all preoperative radiotherapy studies is 5·6% (3·3) with the studies separated and 5·9% (3·4) when the combined groups are compared with the control group.

A more important point is that the subgroup analyses should be confined to the 2954 patients in studies of biologically effective doses of 30 Gy or more with local recurrence data. There was no apparent treatment effect at lower biologically effective doses and inclusion of these groups would dilute any real subgroup differences (ie, add noise without signal). Again, however, inclusion of the 1616 patients in these groups does not alter the findings that the net benefits are greater for younger and for higher-risk patients.

We agree with Ralph Moss that the benefits of radiotherapy in preventing recurrence and death from rectal cancer need to be balanced against short-term and long-term adverse effects. However, we believe that the available data suggest that the benefits from adding radiotherapy to surgery for rectal cancer probably outweigh the negative consequences for many patients. Radiotherapy, at adequate preoperative doses, significantly improved overall survival, even though some of the included trials used outdated—and hazardous—radiation techniques. Thus, although an extension of life has not been the primary aim of radiotherapy, modern techniques that deliver radiotherapy more accurately will probably produce a net survival benefit. Long-term follow-up of late effects in recent trials is needed to be sure, but adverse effects on quality of life so far seem mild.[1,2]

Finally, we believe that most patients offered radiotherapy for rectal cancer are adequately informed about the potential negative consequences as well as the established benefits. It would not be helpful to list the postradiation symptoms cited by Moss, however, since they are hardly ever seen with the doses used to kill microscopic disease that might be left after apparently curative rectal cancer surgery.

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Calcification in chronic renal failure

Sir—In his Oct 6 commentary on vascular calcification in chronic renal failure (CRF), William Goodman[1] discusses the unusual syndrome commonly known as calciphylaxis. He correctly reminds us of the experimental origin of that name and of why it is inappropriate for this syndrome of subcutaneous and skin necrosis associated with vascular calcification. However, his comments on the latter disorder require correction.

In this syndrome, the primary vascular lesion that is directly linked to the necrosis is calcification of resistance-type arterioles in the subcutis. It is quite different from Monckeberg's sclerosis of muscular arteries, which can be seen without CRF. Thus, the calcific uraemic arteriolopathy described by Coates and colleagues[2] is a more specific designation for this lesion in CRF, and not simply a broader term, as Goodman claims. The lesion is silent, but since it is accompanied by intimal thickening, sometimes severe, it contributes in a major way to the clinically dramatic ischaemic infarcts of the subcutaneous fat and skin with ulcerations.

The infarcts vary in distribution—typically in the mid-body (proximal), lower extremities (distal), or both, and rarely, in hands and feet. Dry gangrene of toes and fingers due to arteriosclerotic lesions, whether calcified or not, may coexist with the syndrome lesions.

Goodman makes no mention of the role of obesity. Bleyer and colleagues[3] have clearly shown that morbid obesity is a risk factor for the mid-body and