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Fears over radiotherapy fractionation regimens in breast cancer

Proposed UK trial needs to define techniques as well as numbers of treatments

In the early 1920s Regaud discovered the benefits of radiation treatment fractionation—that is, splitting the dose into several treatments over several days—when he was trying to sterilise the testes of rams with radiation without necrosing the scrotal skin.[1] During the 1930s radiotherapy changed from a dangerous mystery that put patients and staff at risk[2] to a therapeutic modality with a scientific basis. This was an era when radiotherapy fractionation and treatment guidelines were empirically developed from clinical observation tempered by pragmatic issues such as machine availability. Since then the science of radiotherapy has advanced considerably, but suspicions that pragmatic considerations still weigh too heavily are surrounding a proposed British trial of radiotherapy fractionation in breast cancer.

Early randomised clinical trials in cancer—and, therefore, in radiotherapy—reflected the management arguments of the time and addressed questions about what patients to treat with which modality. Trials of radiotherapy process—techniques, fractionation, overall treatment time—had to wait until the 1970s, when radiobiology was suggesting that these factors were crucial. In 1978 Withers showed for pig skin that acute radiotherapy reactions were worse after large numbers of small dose fractions than after a few high dose fractions, while the late reactions were worse after the latter.[3] Therefore, side effects depended on total dose and fraction size. Other evidence suggested that tumour cells could repopulate a tumour rapidly during radiotherapy. Hence, prolonging treatment could be dangerous. Taken together these findings led to a spate of fractionation studies addressing hyperfractionation (more than one treatment a day) and accelerated fractionation (shortened overall treatment time and increasing the number of fractions a day) in mainly pelvic, head and neck, and lung cancers.

A radiotherapy prescription takes into account the tumour type, the volume of tissue to be irradiated, the normal tissue included, and the tissue's tolerance to radiotherapy. It is generally accepted that fraction sizes significantly over 2 Gy may lead to increased late side effects, depending on the tissue, volume, and total dose. In breast cancer the total dose required to eradicate microscopic disease is 40-50 Gy in 15-25 fractions. This dose may be increased for macroscopic disease or for areas at higher risk of recurrence, such as excision areas after breast conserving surgery.

A problem facing British clinical oncologists and their centres is the increasing demand for radiotherapy because of an increase in breast conserving surgery. Those centres traditionally used to a three week regimen also face pressures to consider the internationally more popular five to six week regimens. While consultant posts may have increased to accommodate restructuring of both cancer services and registrar training, provision of equipment and funding of support staff may have lagged behind.

Reviews of radiotherapy practices for breast cancer in the UK still show variation—in dose, fractionation, and areas irradiated.[4 5] To address this variation and the pressures on workload the UK Coordinating Committee on Cancer Research is proposing a trial of "standardisation of breast radiotherapy" with the aim of testing "the effects of radiotherapy schedules using fraction sizes larger than 2 Gy in terms of normal tissue responses, locoregional tumour control, quality of life, and economic consequences." The protocol is being scrutinised by an international data monitoring committee.

Concerns about breast radiotherapy fractionation and techniques have already been fuelled in Britain by the serious (though rare) cases of brachial plexus neuropathy after breast cancer radiotherapy.[6 7] In relation to this latest trial patient advocates are concerned about the use of "high dose fractions," the perceived lack of control of what is irradiated, and a trial that addresses funding—or underfunding—issues.

The draft protocol describes two trials, A and B. B compares two regimens (50 Gy in 25 fractions in 5 weeks versus 40 Gy in 15 fractions in 3 weeks), both of which have been used for some decades in Britain. A uses 50 Gy in 25 fractions as a control to compare with two regimens with high dose fractions: 42.9 Gy in 13 fractions in 5 weeks and 39 Gy in 13 fractions in 5 weeks. To the investigators' credit, an extensive and prolonged pilot study has been performed with detailed early and medium term morbidity analysis.

The trial requires a quality assurance programme based on a site visit but permits variations of treatment planning protocols, though each centre must be consistent internally. Treatment delivery to the lymphatic areas is more clearly defined, no doubt a lesson learnt from the brachial plexopathy review.[6]

Are these trials ethical, valid, and needed? Between them the two trials will study four regimens, yet only

BMJ 1998;317:155–6

the two in B are in common use.[4] A review of treatment variations in the South Thames region showed that approximations of the other two account for only 18% of prescriptions.[5] These latter two regimens of alternate day treatment in 13 fractions over 5 weeks seem to add nothing to patient convenience, bar omitting two attendances and giving alternate days off; are still spread over five weeks; and will have negligible impact on workload compared with 15 fractions.

The inclusion of these two regimens of 13 fractions would contribute data to the radiobiological debate over dose, dose per fraction, and effects on tumour control and morbidity. It may also be justified as an attempt to achieve the aim of "standardisation," although it would standardise only dose and fractionation. Nevertheless, it is not clear why these relatively underprescribed regimens are chosen in preference to commoner variations such as 45 or 46 Gy in 20 or 23 daily fractions over 4-4 ½ weeks.

Some centres and clinicians could be encouraged to participate by trial A, which has three options, and for those currently favouring a 13 fraction regimen, two thirds of patients will be randomised to that, making less impact on workload during the trial. Hopefully, however, these regimens have not been selected simply to achieve maximum accrual by ensuring that potential participating clinicians will not be discouraged by a need to change much cherished practices.

It is valid to compare two well established regimes (trial B), even though radiation oncologists in countries where payment is received per treatment or where there is a fear of exceeding 2 Gy per day would baulk at this. Prolonged experience suggests that trial B is safe, appropriate, and needed and should address all physical, psychological, and economic sequelae. The investigators are to be congratulated for seeking to address this question scientifically, but must ensure a high level of compliance with an agreed protocol that covers not only dose and technique but also what areas are treated and in which circumstances.

The international review committee is spending a considerable time deliberating over these trials, presumably because of the concerns of consumers and clinicians. While an attempt to standardise dose and also fractionation may be commendable, the other issues of concern—what areas are irradiated and how—must also be clearly addressed in the protocols and the quality assurance checks. This may discourage some clinicians from participating but would allay the fears raised by patients and some clinicians, the plexopathy reviews,[6 7] and the lack of a standard approach to peripheral lymphatic irradiation.

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A national target for reducing suicide

Important for mental health strategy as well as for suicide prevention

The mental health target in the green paper *Our Healthier Nation* is "to reduce the death rate from suicide and undetermined injury by at least a further sixth (17%) by 2010, from a baseline at 1996."[1] The former government's *Health of the Nation* strategy included two suicide targets—namely, a 15% reduction in the overall suicide rate and a 33% reduction in the rate in the severely mentally ill.[2] The initial suicide targets were controversial, argument centring on the advisability of a target for a relatively uncommon event (about 5000 suicides and open verdicts each year in England and Wales), the difficulty of predicting suicide, and the pressure the targets might place on psychiatric services. Nevertheless, the overall suicide rate has declined since the original targets were set. Most importantly, the previous rapid rise in suicides in men aged 15-44 years has started to reverse.[1] Why do we still need a suicide target and can suicide rates be reduced further?

Suicide is usually the tragic end point of various possible pathways, influenced by mental ill health and psychological, socioeconomic, familial, interpersonal, and genetic factors. Media influence and the availability of means of suicide also seem to be important.[3] These pathways embrace many factors relevant to mental health in general, and a suicide target is therefore a valuable peg for a range of mental health strategies. Suicide prevention is not, however, solely the concern of mental health services. Some two thirds of all people who commit suicide have not received specialist psychiatric care in the year before death.[4]

A focus on suicide is directly relevant to mental health strategy in primary care, especially improved detection and treatment of depression, even if general practitioners rarely experience suicide in one of their patients. Moreover, it is directly relevant to social health and economic policy. Lastly, it is a solid target that will keep mental health in the forefront of planning about health care and prevention of ill health. The difficulty of measuring the third *Health of the Nation* mental health target—namely, improvement in the health and social functioning of the mentally ill (and indeed the second suicide target[2])—should warn against having another target that lacks hard longitudinal data. While a target related to effective detection and treatment of

BMJ 1998;317:156–7

depression might seem ideal, given the incidence of depression and its consequent disability, it is difficult to imagine what this might be. An unmeasurable target could harm mental health strategy.

If the suicide target is retained in the forthcoming white paper how might it be achieved? Pinpointing factors that have contributed to the recent decline in the suicide rate is not easy. Nevertheless, the management of patients with psychiatric disorders has improved in terms of clinicians maintaining continuity of care through the care planning approach and in the development of more effective medication for schizophrenia and safer antidepressants. The presence of a suicide target has certainly helped keep risk assessment at the forefront of clinicians' minds. One way of refining prevention efforts would be to target specific groups of individuals at risk.

Three immediately come to mind. Firstly, the rate of suicide in young men is nearly double what it was 10-15 years ago. Creative strategic planning is necessary to tackle the anomie and substance abuse that afflict many young men today, especially in socioeconomically deprived groups. Secondly, patients who deliberately harm themselves have a risk of suicide some 100 times that of the general population,[5] and 20-25% of people who die by suicide have presented to a general hospital after episodes of self harm in the year before death.[4] Yet despite the availability of guidelines,[6] the quality of general hospital psychiatric services for these patients remains variable and often inadequate.[7] When many people who will commit suicide are presenting to clinical services this must be a focus for improvement, even if demonstrating effectiveness in terms of suicide prevention is difficult.[3] The third group comprises patients with mental illness: virtually every psychiatric disorder carries a raised risk of suicide. Further developments in mental health services must, however, be introduced in ways that encourage clinical creativity and competence without adding to the stifling sense of medicolegal liability that afflicts many clinicians in psychiatry today.

Effective suicide prevention should combine population strategies with those aimed at high risk groups.[8] Population strategies should include restricting the availability of means of suicide, since reducing availability does seem to reduce risk[3]; standards for media reporting and fictional portrayal of suicides; and, possibly, school programmes for equipping youngsters with effective problem solving skills and helping staff to detect those at risk of mental health problems and self harming behaviour.[9] Finally, while showing the effectiveness of crisis intervention helplines such as the Samaritans is difficult, the Samaritans should continue to receive support. Recent efforts to extend the availability of Samaritan befriending to reach those at risk, including in prisons, rural areas, and via email, deserve praise.

Abandonment of a suicide target at a time when other countries are establishing suicide prevention programmes[10] would be a backward step, not only for future potential suicides. Absence of a clear and measurable mental health target, for which suicide seems the only realistic candidate, could have negative consequences for overall mental health strategy and is likely to result in the needs of those with mental ill health slipping backwards in the league of health priorities.

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Capital charges: a tax on the NHS

Worse may follow as NHS assets are privatised

Under the new national framework for assessing performance in the NHS trusts will be compared partly on the basis of their costs per unit of care and of the productivity of capital estate.[1] Unit costs and productivity of capital are crucially influenced by two factors: the capital charging system under which the government plays shareholder and banker to the NHS, recovering a 6% return on all capital used by the NHS,[2] and the current and future purchasing decisions of primary care groups. Other changes, however—notably, the private finance initiative and the freedom of primary care groups from capital charges—raise questions about the appropriateness of these measures of efficiency.

The main argument for the introduction of capital charges in 1992 was that NHS assets were being used inefficiently. Requiring NHS trusts to pay interest and dividends on their assets, and to recoup those costs through the prices charged to purchasers, would, it was argued, lead to greater cost effectiveness and allow comparisons to be made between the NHS and the private sector.[3] This, however, relies on two arguable premises—firstly, that an NHS provider is sufficiently similar to a commercial enterprise that the imposition of a private sector financial regime will lead to greater efficiency; secondly, that NHS capital charges realistically represent the cost of the buildings and equipment needed to deliver services.

BMJ 1998;317:157–8

Taking the latter premise first, NHS assets are valued at current value for land and current replacement cost for buildings, plant, services, and equipment rather than at historic cost (which would be the usual practice in the private sector). The effect of this overvaluation of assets is to make capital charges (paid from the trust's revenue) cripplingly high. The 6% rate was chosen "to ensure that there is no inefficient bias against private sector supply"[4] and not to reflect the real cost of capital to government. Bringing public sector capital accounting in line with private sector conventions in respect of returns on capital makes the substitution of private for public provision a logical move since it disguises the most significant differences between the two sectors.

What of the incentives for efficiency supposedly created by capital charges? The effect of the system on individual trusts depends on the relation between their income and the asset base on which they pay capital charges: the greater the proportion of a trust's income taken up by capital charges, the greater the risk of financial non-viability.[2] On average NHS trusts are paying out 9% of their annual revenue income on capital charges. Only two options exist for adjusting the income:asset ratio: increasing income or reducing assets.

To increase income trusts can compete for market share with other NHS providers or attract private sector income. Competing for market share destabilises neighbouring NHS providers because, without expansion in purchasers' budgets, trusts can gain only at the expense of other providers.

Trusts can reduce their assets through disposing of them or taking facilities out of service. This has led to capital charging being compared to a "windows tax," with facilities being withdrawn to avoid charges.[5] A more radical approach is to liquidate all assets (and thereby avoid paying capital charges altogether) through public-private partnerships and the private finance initiative. Under the private finance initiative NHS assets and land are sold or transferred to private sector consortia which design, build, and operate new hospitals. The NHS becomes a tenant, leasing back the premises and services for 30-60 years.[6] Payments for the lease of the new hospital and services are financed by land sales, government subsidies,[7] and, crucially, the capital charges paid by NHS trusts. As they are not public sector assets, private finance initiative hospitals will not be liable for capital charges, but the equivalent of the trust's current capital charges will still enter into the prices charged each year to purchasers.

This has created a leak of NHS funds from the public to the private sector. Previously the capital charge "returns" the Treasury received from NHS trusts (around £2.5bn a year) were passed to the Department of Health, which included them in health authorities' revenue allocations for hospital and community health services.[8] They then entered into payments to NHS trusts, which made returns to the Treasury, thus closing the circle. When NHS services are provided by the private sector, which does not pay capital charges to the Treasury, the funding leaves the system, reducing the annual circulating fund out of which other trusts must make their returns. Unless there is a concomitant increase in NHS revenue to offset this leakage—and so far there has not been—this will lead to the bizarre phenomenon of privately financed hospitals being funded through what is in effect a tax on hospitals in public ownership.

Ironically, the use of the private finance initiative has the potential to increase unit costs since it increases the amount of income that goes on buildings and equipment even while cutting capacity. Bromley Hospitals Trust's projected private finance initiative lease payments represent 14.7% of its current income, compared with the 11.4% it currently spends on depreciation and capital charges, despite the fact that the trust will reduce acute beds by a fifth.

The shifting of services from acute and community hospitals to the primary sector will have the same effect. General practitioner fundholders (and future primary care groups and primary care trusts) are free of the capital charging regime of the NHS. Since the introduction of fundholding an increasing number of general practitioners are either undertaking, or contracting with the private sector for, services formerly carried out by NHS trusts.

Current policies on disposing of NHS assets and introducing primary care trusts will accelerate these trends. All NHS assets deemed surplus to requirement have to be offered first to other NHS bodies. Around the country fundholders with private sector backing and NHS revenue are buying up this surplus NHS estate. As primary care trusts develop, general practitioners with a cash limited budget may be tempted to mortgage NHS community trust sites to the private sector under private financing arrangements and to gain a commercial stake in the enterprise. The transfer of NHS assets to private ownership and management is, of course, ultimately funded from NHS revenue. The effect will be to create serious financial instability in NHS trusts and potential for enormous inequities in access to service provision.[9]

Concerns about the potential effects of public-private partnerships and primary care trusts are not misplaced. The direction of current policy suggests that in the medium term many NHS assets will transfer to private ownership. The question is whether, as with long term care, liquidating public sector assets will be followed by the privatisation of the costs of care.[10]

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Vaccination and its adverse effects: real or perceived

Society should think about means of linking exposure to potential long term effect

Vaccines have been spuriously linked to sudden infant death syndrome,[1] paediatric asthma,[2] autism,[3] inflammatory bowel disease,[4] and permanent brain damage.[5] Recently US researchers have suggested that vaccination after 28 days after birth may induce type 1 (autoimmune) diabetes mellitus in susceptible individuals.[5] This theory, pounced on earlier this year by the US media, may have led to a lowering of confidence in childhood routine immunisation. In May several institutions (including the National Institute of Allergy and Infectious Diseases, Centres for Disease Control, the World Health Organisation, and the UK's Department of Health) sponsored a workshop at the US National Institutes for Health to assess the evidence of a possible causal link.

Immunologists, diabetologists, epidemiologists, policymakers, and observers debated the available evidence for two days and concluded that it does not support a causal link between vaccination and the onset of type 1 diabetes. Some short and longer term observational studies to test the hypothesis are currently underway. However, the results of a large randomised controlled trial of vaccine against *Haemophilus influenzae* type b carried out in Finland in 1985-7[6] were reanalysed by Tuomilehto et al and showed no association between the incidence of diabetes mellitus and the addition of another antigen to the schedule, irrespective of timing (unpublished data). Data reanalysis was made possible by prospective linking of individual information on exposure (in this case infant vaccination or placebo administration) with the Finnish diabetes register.

Neil Halsey, head of the Institute for Vaccine Safety at Johns Hopkins University, summed up features common to recent vaccine scares:

- A casual link is usually claimed with a disease or condition of unknown or unclear aetiology.
- The association is claimed by one investigator or a group of investigators.
- The association is not confirmed by peers or by subsequent research.
- The claims are made with no apparent concern for potential harm from public loss of confidence and refusal to vaccinate children.

Additionally, findings of subsequent studies that fail to confirm the original claim never get the publicity given to the "original" finding; thus the public never gets a balanced view.

It is time to think hard about how society can deal with the difficult issue of possible long term and rare adverse effects of vaccination. Attention to the issue is unlikely to fade, as new and better vaccines are produced and as public expectations of effective and safe interventions increase. The first obvious source of data on rare and long term effects is the original clinical trials of the vaccine, with direct observation of the incidence of events in one of the double blind randomised arms. But, early trials, usually conducted for registration, are too small and too short.[7] Additionally, assessment of adverse effects is probably best done by comparing events in one or more intervention arms with those in a placebo arm, thus restricting observation to trials of new or partially tested vaccines for which a placebo arm is ethically admissible.

One possible solution could be to increase the duration and power of trials to detect rare and long term adverse effects. Apart from cost, however, there are major ethical problems in continuing a trial with a non-immunised cohort in an effort to detect possible rare and long term effects once the short term safety and effectiveness of the vaccine have been shown.

The use of case-control studies and case series is helpful in defining the likelihood of an association but, given the possible presence of multiple unknown biases, such studies do not allow estimation of the attributable risk, essential for safety assessment. An additional problem with any prospective approach is that some adverse effects become known only years after the development, marketing, and registration of the vaccine, making "data dredging" the only way in which they might be observed and later recognised. Data dredging is likely to be inefficient and unable to assess unexpected associations, which are likely to take place periodically.

One way out of the dilemma could be the linking of individual exposure to vaccination to possible adverse events in later life in a similar fashion to the reanalysis by Tuomilehto et al of the original *Haemophilus influenzae* type b trial data. This would allow the creation of retrospective exposure cohorts linked to historical controls for testing any of the hypotheses generated. This approach would require access to individual immunisation data and the ability to identify and locate individuals in later life. As most immunisation schedules vary from country to country the international extension of such a scheme would allow comparisons based on exposure to different schedules, thus enhancing the power of the system. An enhancement of this method could be its use within the context of a systematic review of the known effects of vaccines in question made available within the Cochrane Library.

Whatever methods are used, governments and manufacturers will be increasingly involved in assessing long term adverse effects of vaccines and will need to reassure the public of the overwhelming safety record of vaccines, when the seriousness of the target disease is forgotten. This at present is the only certainty.

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BMJ 1998;317:159–60

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Chiropractic for low back pain

We don't know whether it does more good than harm

Chiropractic includes various techniques used in the hope of correcting vertebral disc displacements, freeing spinal joint adhesion, inhibiting nociceptive impulses, or correcting spinal misalignment. Several national guidelines on the treatment of low back pain recommend spinal manipulation, including chiropractic, as a symptomatic treatment for acute uncomplicated cases where pain fails to resolve spontaneously within the first months.[1] How solidly are these recommendations based on evidence?

There are many controlled trials of spinal manipulation and no fewer than 51 reviews.[2] Surprisingly, in the review of Shekelle et al,[3] which provided the basis for the recommendations mentioned above, the subset of randomised clinical trials on acute low back pain which generated these favourable recommendations did not contain one single trial of chiropractic. A recent systematic review restricted to chiropractic manipulation included only eight randomised controlled trials, all of which were methodologically flawed and "did not provide convincing evidence for the effectiveness of chiropractic for acute or chronic [low back pain]."[4] Consequently, we can conclude only that the effectiveness of chiropractic as a treatment for low back pain has not been established beyond reasonable doubt.

Is chiropractic safe? Cervical manipulations are burdened with severe adverse reactions, such as vertebrobasilar accidents and paralyses due to fractures.[5] A literature review identified 165 vertebrobasilar accidents, including 29 deaths.[5] Estimates of their incidence range from 1 per 200 000 to 1 per million cervical manipulations.[5] A patient survey suggested that about 12% of users experience (mostly mild) adverse reactions.[6] Mild adverse reactions were also reported after one third of all treatments in a prospective study.[7] The risks of manipulating the lower spine seem to be lower, with fractures and cauda equina syndrome being the most serious reactions.[5] Nevertheless, upper spinal manipulation is also occasionally performed in lower back pain. Finally, there may be important indirect risks associated with chiropractic. Potential overuse of radiographs by chiropractors is one example[8]; another is the negative attitude of some chiropractors towards immunisation.[9] Thus, even if chiropractic manipulation were totally devoid of risks, the approach of chiropractors may not always be so.

Lastly, does chiropractic save money for healthcare systems? There are few conclusive economic evaluations, but most of the rigorous studies do not suggest that chiropractic saves money. A study comparing the costs of care by chiropractors, primary care physicians, and orthopaedic surgeons in the United States indicated that the total direct outpatient cost per episode of low back pain was highest for urban chiropractors.[10] One obvious reason is that, on average, chiropractors use more consultations per episode of back pain than other professionals.[11] However, studies with other designs sometimes provide the opposite results.[12] A review of workers' compensation studies concluded that "chiropractic cost-effectiveness is not yet convincingly proven."[13]

On the basis of current evidence, it seems uncertain whether chiropractic does more good than harm. More and better research is required.

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BMJ 1998;317:160

Correction

Getting evidence into practice

An error occurred in this editorial by Fiona Godlee (4 July, p 6). Gina Radford was wrongly described as director of the National Institute for Clinical Excellence. She is head of the public health development unit at the Department of Health; the director of the institute has yet to be appointed.