An approach to randomization into surgical clinical trials

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The authors have no conflicts of interest to declare

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Recruitment of patients into surgical trials is difficult. One in five surgical randomized controlled trials is discontinued early and one in three trials remains unpublished.[1] This is particularly problematic when a study has a surgical and a non-surgical arm and in the multi-modal treatments that include surgery in many cancer trials. There is a recurring sticking point in randomizing patients because of the inherent difference between a preoperative surgical consultation and counselling patients about randomisation. This could be resolved if we accept that there is no necessity for the patient to meet a surgeon until they have been assigned to a study arm involving surgery.

The conventional surgical consultation

A surgeon meeting a patient has already had access to all the relevant data including definitive imaging, often based on a multidisciplinary team meeting. When the patient enters the room, the surgeon will have already narrowed the agenda to the issues that pertain to this patient. Risks and benefits must be explained and all realistic options presented. More thought and further information may be needed but the core purpose of the consultation is for the surgeon and the patient to reach an understanding of the best way ahead and to build mutual trust. This is an important and rewarding aspect of surgical practice.

Counselling for randomisation

The context is again a patient whose clinical situation has been thoroughly investigated. The treatment options have already been explained and the patient has been introduced to uncertainty about the best way forward. It has been agreed in a rigorous process of clinical trial design, peer review and ethical analysis that the best way to resolve that uncertainty is by randomization into a controlled trial. The counsellor for randomization has to be able say “I

do not know which of the two treatments you will have." All subsequent questions such as "Which do you think is better?" or "If you were me which would you have?" must be gently but unequivocally deflected.

Surgeons' and patients' perceptions

These very different scenarios require different mind sets. The surgeon may find it impossible to dissemble by not offering an answer to all the patient's questions; the person randomizing has to avoid giving advice that might induce bias. The surgical consultation is designed to rationalize choices reflecting benefits, risks and the patient's wishes; randomization abrogates choice. It is hardly surprising that surgeons' attempts to recruit into trials often fail. Expressing uncertainty may feel uncomfortable in a conversation during which the surgeon is accustomed to help the patient in making this life changing decision, building confidence and mutual trust. Patients do, however, understand uncertainty. Many want to be involved in research. They should be given a fair chance to join the trial.[2]

Perhaps the problem is that the profession has tackled this in the wrong order. It seems rather obvious that the surgical consultation and the randomization meeting would be better separated. If that is accepted then they could be in the reverse order. Once a patient has a treatment assigned, the uncertainty is resolved or at least externalised and the surgeon can get on with discussing the implications of the *assigned* treatment. It is perhaps a bit like choosing a house: after all the soul searching and weighing up of pros and cons, some arbitrary event determines the choice of house. It then becomes easier to come to terms with living in it. This is not a very radical proposal. There are precedents for the surgical consultation to be after the treatment has been assigned which work in practice.

In many trials, the procedure is not separable from the surgeon. The surgeon frequently struggles with equipoise, particularly when randomizing a patient to a less preferred or less well practiced technique.[3] When a trial compares radiotherapy versus surgery for example, expertise based randomization is inescapable. In both of the above circumstances, the patient should only meet the surgeon after the treatment arm has been allocated. In the prostate cancer trial, ProtecT, if men had a PSA of 3.0-19.9ng/ml and prostate cancer on biopsy, they were seen in a 'diagnostic' clinic by a clinician. If they had clinically localised disease and no significant co-morbidity, they received a second 'information' appointment and were counselled for randomization by the research nurse. It was only after this stage that they met the surgeon or radiotherapist depending on the arm already assigned.[4,5]

Ethics of randomization

Cancer trials that commit one group of patients to an intervention compared to 'watchful waiting' are particularly challenging. It has been a common experience in the pulmonary metastasectomy in colorectal cancer trial, PulMiCC[6], that despite being convinced of the need for the trial, surgeons find randomization difficult. It may feel almost 'unethical' to continue monitoring a lung metastasis following randomization by another agency when all the surgeon's instincts are to do an operation to take it out. Much the same is true of so-called complete responses based on imaging, visual appearances and biopsies in cancer trials based on non-surgical therapies. Chemoradiotherapy for oesophageal cancer is a good example, where a third of such responding patients are found to have residual cancer within a resection specimen. The surgeon finds it difficult to accept that these patients may derive little survival benefit from oesophagectomy and at the cost of significant reduction in quality of life.

As stated in a letter to the Lancet back in 1999: *"Call randomized trials difficult, very difficult, or nearly impossible to do—but please do not call them unethical. It is the uncontrolled experiments that perpetuate unproven and potentially harmful treatments."*[7] We are bound by rigorous independent processes which test the ethics of a trial. Once the trial is running it makes sense to be clear about the duties of participants who have signed up, and to sequence the tasks to make the trial possible.

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