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Surgeon knows best versus breast cancer surgical clinical trial equipoise: A plea for the sake of future trials

Short Title: Equipoise in Surgical Clinical Trials

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Equipoise is the central concept of clinical trials. By opting to participate in a trial the treating team clearly thinks that the study question is important and relevant. It implies that the team believes that either management strategy may be better and that higher-level evidence is required before practice is consolidated, leading to better outcomes for that cohort of patients.

Most medical oncology trials are comparing a new systemic therapy or combination of treatments with the current standard. This is based on biological plausibility developed in the laboratory and then early phase data suggesting that the new regimen may result in improved overall survival with acceptable toxicity. Often the new systemic treatment is only available (or affordable) as part of the clinical trial. Surgical oncology phase 3 trials are usually different. Nowadays they frequently address the question of whether a less radical intervention will lead to similar locoregional control as the standard intervention, with less morbidity. Overall survival is often a secondary endpoint. These differences between medical and surgical oncology trials have various implications, and generally mean that recruitment to surgical trials has separate challenges.

Most surgical clinical trials are investigator led, and so securing funding means that the time from concept to implementation is longer than for Pharma supported trials. Once funded and ready to open, the sponsor of the trial identifies participating institutions based on an expression of interest from

investigators at a potential site stating that they have equipoise, adequate suitable patients and the resources to participate. The sponsor then expends significant time and money to open at the selected sites. This all sounds sensible and productive but all too often surgical trials recruit fewer than predicted cases and the issue of investigator selection bias creeps in, challenging the fundamental notion that the treating team have equipoise regarding the study question.

Clearly eligible patients can make a choice to have a particular treatment or choose to be randomized on the clinical trial. Conversely if the trial is open and the patient is eligible then the surgeon has an ethical obligation to discuss the trial as part of their informed consent and explain why it is ethically acceptable for the trial to be happening. It is not like a drug trial where the new treatment may only be available on trial. In surgical trials either of the operations can be done. The information on which the decision is made generally comes from or is interpreted by surgeons who stereotypically have definite views (i.e. equipoise with exceptions), and are practiced in the art of persuasion. It is critical that the surgeon and other members of the trial team do not lead this decision-making process by colouring discussion with personal biases. If this happens then only those patients that fit the individual investigators' prejudices will be enrolled in the study, limiting the applicability of the results of the study, and leaving the eventual findings of the study open

to critique. This in turn may mean that the study does not resolve the question being addressed.

Many national and international surgical trials have taken too long to commence, failed to accrue the predicted number of cases, closed early with incomplete recruitment or dragged on for years without full accrual. In some cases the delays and poor recruitment has meant that the initial study question has become somewhat irrelevant as the standard practice has moved on by the time results are published. There are several examples of the issues discussed above in recent breast cancer surgical trials related to sentinel lymph node biopsy. These include Sentinel Node or Axillary Clearance (SNAC1), SNAC2, International Breast Cancer Study Group Trial 23-01 and American College of Surgeons Oncology Group (ACOSOG) Z0011.[1-5]

The ACOSOG Z0011 study compared completion axillary clearance with no further axillary surgery for patients undergoing breast-conserving surgery (BCS) who had limited disease in one or two sentinel nodes and found no differences in outcomes. It has been particularly challenging to interpret, with North American guidelines and many North American cancer centres accepting it is a practice changing study and that no further axillary therapy is required for patients meeting the study criteria, whereas Australian practice has not followed this lead [5]. The Australian and New Zealand interpretation

is that while the ACOSOG Z0011 data are provocative, but as the study was severely limited by the highly selected patients and inordinately slow accrual as well as variable radiotherapy fields, they are not sufficiently robust to form the basis for changing long-held practice.

The Australian and New Zealand Breast Cancer Trials Group (ANZBCTG) and Breast Surgeons of Australia and New Zealand Inc. (BreastSurgANZ) are now participating in the UK led POSNOC Study.[6] This study randomizes eligible BCS or mastectomy patients with macrometastasis (i..e. ≥2mm deposit) in one or two sentinel nodes to adjuvant therapy alone vs adjuvant therapy and additional axillary treatment with either surgery or radiotherapy. This study was established after recognizing ongoing equipoise on the subject amongst many UK and ANZ surgeons. It is designed to address the weaknesses of the ACOSOG Z0011 study and to provide extra independent high quality data to inform this critical aspect of breast cancer treatment.

This is a plea to Australian and New Zealand POSNOC investigators to put aside your intrinsic biases and discuss with true equipoise the uncertainties surrounding this clinical situation with all your eligible patients. Please do not let this important trial be criticized for selection bias and slow accrual. Circumstances may exist with extreme cases where the multidisciplinary team requires completion axillary dissection to facilitate decision-making but these cases are few and far between. Please heed the lessons of the past with

regards this and other surgical clinical trials for the sake of our present and future patients.

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