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Overview

Recommendations for Randomised Trials in Surgical Oncology

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Abstract

Trials of surgical procedures in the treatment of malignant disease face a unique set of challenges. This review aimed to describe recommendations for the design, delivery and reporting of randomised trials in surgical oncology. A literature search was carried out without date limits to identify articles related to trial methodology research in surgery and surgical oncology. A narrative review was framed around two open National Institute of Health Research portfolio trials in colon and rectal cancer: the STAR-TREC trial (ISRCTN14240288) and the ROCCS trial (ISRCTN46330337). Twelve specific challenges were highlighted: standardisation of technique; pilot and feasibility studies; balancing treatments; the recruitment pathway; outcome measures; patient and public representation; trainee-led networks; randomisation; novel techniques and training; learning curves; blinding; follow-up. Evidence-based recommendations were made for the future design and conduct of surgical oncology trials. Better understanding of the challenges facing trials in the surgical treatment of cancer will accelerate high-quality evaluation and rapid adoption of innovation for the benefit of patient care.

Key words: Colorectal cancer; oncology; patient and public representation; research methodology; surgery; randomised trials

Statement of Searches

A narrative review was synthesised, describing challenges and recommendations for the design, delivery and reporting of randomised trials in surgical oncology. A literature search was carried out using PubMed and OVID via Medline, with the MeSH terms ‘surgical’ OR ‘surgery’ OR ‘surg*’; AND ‘trial’ OR ‘randomised’; AND ‘methodology’ OR ‘design’ OR ‘conduct’ OR ‘recruitment’ OR ‘reporting’ (last accessed: 1 June 2017). No date restrictions were imposed. Non-English language papers were excluded. The ‘related articles’ function, references and citation lists were used to identify additional relevant content.

Introduction

Trials in surgical oncology are characterised by the evaluation of surgical or interventional procedures in at least one treatment group. They include patients undergoing curative or palliative treatment for malignant disease. The complexity of trials involving surgical interventions has historically led to a paucity of randomised evidence in the surgical management of cancer [1,2]. Unique challenges arise in each phase of the research pathway; from protocol design to the recruitment consultation, randomisation, blinding, standardisation of the experimental intervention, outcome selection and assessment, ethics and reporting. This has led to a failure to recruit patients into surgical trials [3], introduction of bias [4], discontinuation of trials [5] and misreporting [6–8].

Twenty years ago, a systematic review showed that the proportion of treatments supported by randomised evidence in surgery was almost half that of general medicine

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[9]. Efforts to better understand this complexity have improved the quality and volume of surgical trials since this time. Specific recommendations have been made to improve the way surgical trials are designed, delivered and reported [10], but a number of practical difficulties persist. This review describes contemporary recommendations in the design, conduct and reporting of randomised trials in surgical oncology.

Materials and Methods

The review framed around two examples of surgical trials in colon and rectal cancer from the National Institute of Health Research portfolio [11]:

(1) STAR-TREC: Can we save the rectum by watchful waiting or transanal surgery following (chemo)radiotherapy versus total mesorectal excision for early rectal cancer? (ISRCTN14240288);
(2) ROCSS: Reinforcement of Closure of Stoma Site. A randomised controlled trial of reinforcement of closure of stoma site using a biological mesh (ISRCTN46330337).

Themes were illustrated with practical examples from the two trials.

Trial Example 1: STAR-TREC

Can we save the rectum by watchful waiting or transanal surgery following (chemo)radiotherapy versus total mesorectal excision for early rectal cancer? (ISRCTN14240288).

Trial Summary

STAR-TREC [12] is a multicentre international randomised, three-arm parallel, phase II feasibility study in patients with biopsy-proven adenocarcinoma of the rectum (IDEAL phase 2b [13]). Patients with rectal cancer, staged by computed tomography and magnetic resonance imaging as $\leq$ cT3b (up to 5 mm of extramural spread) N0M0 can be included. STAR-TREC will assess the ability to recruit to a large, IDEAL phase 3, multicentre randomised trial comparing radical surgery versus organ-saving treatment (Figure 1). Participants are randomised in a 1:1:1 ratio to receive:

(i) conventional total mesorectal excision (TME) surgery (control);
(ii) organ-saving treatment using long-course concurrent chemoradiation;
(iii) organ-saving treatment with short-course radiotherapy.

After the initial organ-saving treatment (ii, iii), the clinical response to (chemo)radiotherapy determines the next treatment step. A complete clinical response leads to a strategy of watch and wait. A good but incomplete response is followed by transanal microsurgery to remove the portion of the bowel wall affected by tumour. Little or no response is followed by TME. The primary outcome in phase II is the ability to increase international recruitment to a level that would sustain a larger phase III study incorporating pelvic failure as the primary end point. This corresponds to four cases per month in year 1, rising to six per month by the end of year 2. A summary of challenges and recommendations can be found in Table 1.

Standardisation of Technique

The Medical Research Council guidance for developing and evaluating complex interventions recommends that investigators 'consistently provide as close to the same intervention as possible' by 'standardising the content and delivery of the intervention' [14]. STAR-TREC compares stable interventions with which surgeons will already have reached a standard of expertise (TME or TEMS (transanal endoscopic microsurgery)). However, significant technical variation can still exist in the provision of these interventions, even within a single hospital. The trial design must strike a balance between a pragmatic design; a real-word comparative effectiveness study [15], allowing technical and non-technical variation in the way in which a surgical intervention and periprocedural care is delivered, and an explanatory approach; a design that requires a homogenous population, strict standardisation of interventions and comparison of efficacy to a placebo or sham group. Variation can occur not only in the tested surgical procedure, but also in the timing and delivery of concomitant interventions; for example, general and regional anaesthesia, chemoradiotherapy and the provision of intensive care support. A complex surgical intervention with multiple components can act interdependently or independently to influence outcomes [16]. In a pragmatic randomised trial, the fidelity of an intervention must be sufficient to ensure that the experimental intervention is being uniformly tested, but not so prescriptive that translation into real-world practice is not possible. Tools such as PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2) have been used to model the 'pragmatism' of a trial across phases of its design and judge the extent to which effectiveness, rather than efficacy, is being tested [17].

A description of the technique is also important to ensure robust meta-analysis [16]. Thirty per cent of surgical trials only report the name of the procedure, without further detail of the procedural steps or standardisation [18]. There are three ways to describe a surgical intervention: (i) by the overall technical purpose of an operation (e.g. removal of the appendix); (ii) by its key component parts; (iii) by the steps within each component part [19]. Direct observation, video-monitoring or semi-structured interviews with surgeons carrying out a procedure can help to define these [20]. For each step or component, it must be decided which are mandatory, prohibited or optional and the degree of flexibility allowed within this structure. These must be described fully in the study protocol, including the context of intervention

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