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Editorial

The SMALL Trial: A Big Change for Small Breast Cancers

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Addressing the overdiagnosis and overtreatment of breast cancer resulting from breast screening has been the focus of considerable media attention, and is an international research priority. Standard treatment involving surgery and adjuvant radiotherapy for small, biologically favourable screen-detected cancers can be associated with significant complications, with few potential benefits for patients. Strategies to de-escalate components of the treatment pathway may address overtreatment and reduce morbidity for patients without detriment to oncological outcomes. This editorial discusses the design and rationale of the SMALL trial, a new study aiming to de-escalate surgical treatment and evaluate minimally invasive vacuum-assisted excision (VAE) as an alternative to standard surgery in this setting.

Addressing Overtreatment within the National Health Service Breast Screening Programme

Since the National Health Service Breast Screening Programme (NHSBSP) was established in 1988, there has been debate concerning the risks and benefits of mammographic screening. In 2010, the Nordic Cochrane Group fuelled controversy by suggesting that there was 'no convincing evidence' that the NHSBSP saves lives [1]. The resulting UK Independent Panel Review of Breast Screening concluded that the NHSBSP did result in a significant reduction in breast cancer mortality, but there was undoubtedly overdiagnosis within the programme [2] and research to address this was strongly recommended. The medical community has embraced this challenge; several trials to reduce overdiagnosis and resulting overtreatment have been designed focusing on de-escalating standard treatment to minimise

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harm. These include trials omitting breast surgery in patients with low-risk ductal carcinoma *in situ* (the UK LORIS, EORTC LORD and US COMET trials), trials omitting axillary surgery in patients with radiologically normal axillary nodes and low-risk breast cancers (the SOUND trial) and trials omitting radiotherapy in patients at low risk of recurrence (PRIMETIME) [3–5]. The SMALL trial aims to de-escalate surgical treatment and evaluate minimally invasive VAE as an alternative to standard surgery for small, biologically favourable, screen-detected breast cancers.

Problems with Current Management Strategies

Screen-detected breast cancers are currently treated with surgical excision (usually image-guided wide local excision) and sentinel lymph node biopsy (SLNB) under general anaesthesia, followed by adjuvant therapies as agreed by the multidisciplinary team. Wide local excision may result in complications [6] and/or poor cosmetic outcomes [7], which may adversely affect the patient's satisfaction and quality of life [8,9]. In addition, up to 20% of patients may require additional surgery for re-excision of margins involved with tumour following histopathological assessment [10]. This has considerable impact on patient well-being and significant resource implications for the NHS [11] and although many international centres now accept the pathological definition of a clear margin as 'no tumour at the inked resection margin' [12], current practice continues to vary across the UK [13].

SLNB is currently standard of care for radiologically node-negative patients, but the incidence of axillary nodal disease in this group is known to be low and ultrasound (with biopsy if indicated) has an extremely high negative predictive value [3]. Even in the context of a positive sentinel node, excellent regional control can be achieved in the axilla without further surgical dissection, suggesting that a low burden of nodal disease can be adequately controlled with adjuvant therapies [14]. Furthermore, information on the extent of nodal involvement does not usually influence treatment selection [15], nor indeed alter long-term prognosis [16]. Data supporting the omission of axillary surgery in selected low-risk patients suggest that this approach is safe, with acceptable recurrence-free survival [17]. Taken together, these data suggest a lack of evidence to justify the routine use of SLNB in this setting, given its attendant (albeit low) morbidity in terms of lymphoedema, numbness and paraesthesia [18].

A Minimally Invasive Approach to Treating Small Breast Cancers

Many of the small, biologically favourable cancers diagnosed by the NHSBSP probably represent overdiagnosis, and recent data suggest that such tumours have an excellent prognosis [19]. Treatment with conventional open surgery has been extrapolated from historical data, and there is no prospective evidence to support this contemporary approach. Minimally invasive techniques could therefore be developed for use in this setting, potentially reducing the morbidity and complications associated with standard treatment, allowing patients to avoid a general anaesthetic. These may also have significant benefits for the NHS, including cost savings associated with the avoidance of surgery.

Vacuum-assisted biopsy (VAB) is one such minimally invasive technique that is widely available in the UK. The VAB device is equipped with a large calibre needle, and the procedure is carried out under ultrasound or X-ray guidance under local anaesthesia during a brief out-patient visit. Initially used for diagnostic purposes, VAB has evolved and is utilised as a tool for non-surgical excision of benign lesions [20,21] as well as the management of (B3) lesions of uncertain malignant potential [22]. It is generally well-accepted by patients [23] and VAE is approved by the National Institute for Health and Care Excellence (NICE) for the excision of benign breast lesions. Post-VAE imaging can accurately estimate the complete removal of masses in 90% of cases [24]. There is, therefore, evidence to support the repurposing of this technique for the excision of small screen-detected breast cancers with favourable biological characteristics.

Study Design

SMALL is a prospective, multicentre, randomised (2:1) phase III trial of minimally invasive VAE versus surgery in patients with small, biologically favourable screen-detected breast cancer. It aims to generate high-quality, practice-changing clinical evidence to support the safe de-escalation of surgical treatment within the context of standard adjuvant radiotherapy and endocrine therapy in selected patients. The study is designed to assess whether:

- The extent of surgical treatment can be reduced in the context of standard adjuvant radiotherapy and endocrine therapy.
- VAE is non-inferior to conventional surgery in terms of the requirement for a second operation to achieve complete resection of the cancer.
- There is an acceptable local recurrence risk in the VAE arm with long-term follow-up.

The primary outcome measures in SMALL are re-excision rates and local recurrence-free survival time. The novel study design incorporates a randomised, non-inferiority comparison of the requirement for a second procedure between the techniques. Single-arm follow-up of the VAE cohort will then allow determination of the local recurrence rate in this group. The trial schema, including key eligibility criteria, is shown in Figure 1.

Secondary outcomes will assess the psychological impact of VAE compared with standard surgery. A full economic analysis is also included within the design to determine the cost-effectiveness of the technique. SMALL requires the

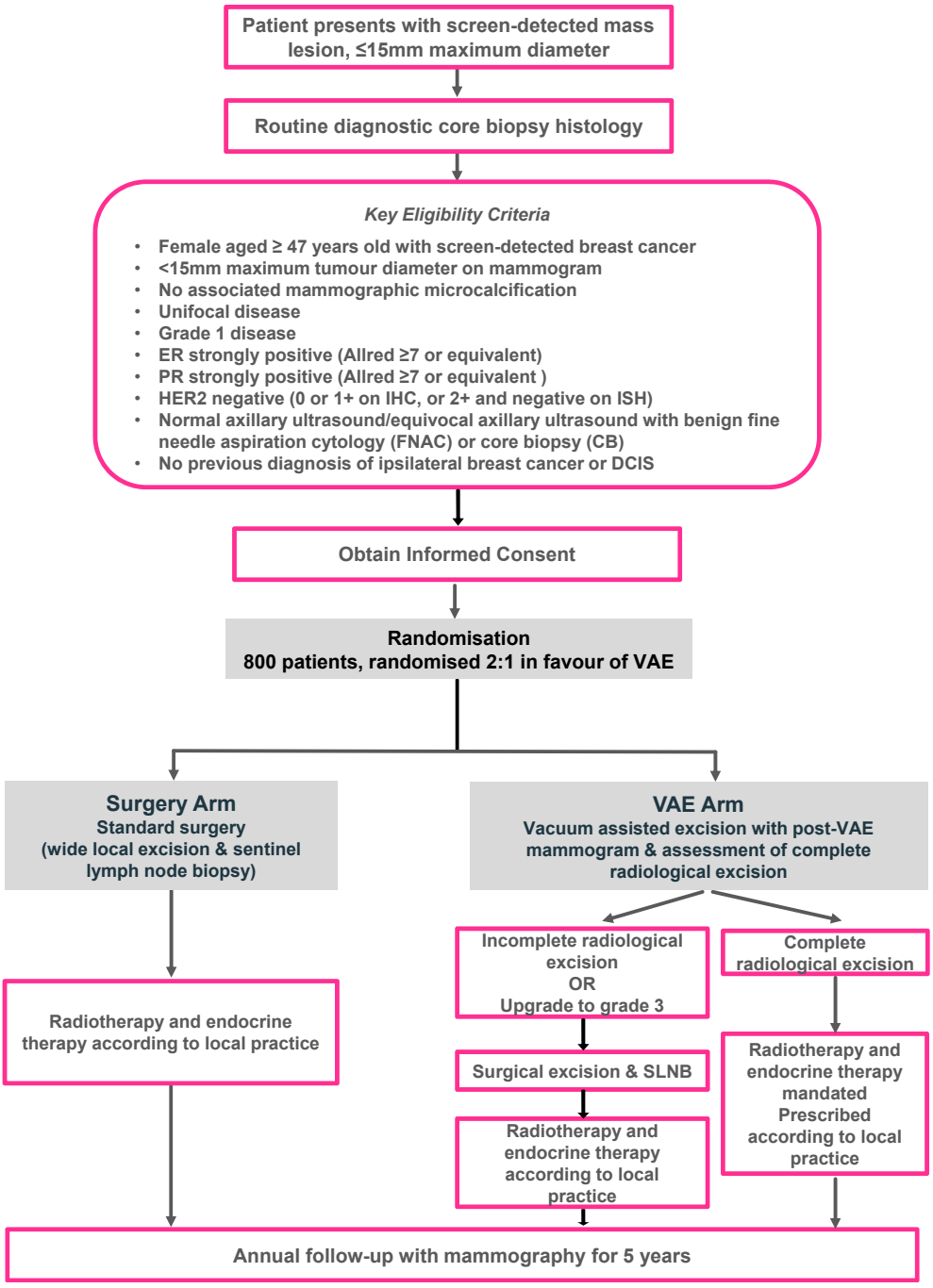

Fig 1. SMALL trial schema.

recruitment of 800 patients over a 4-year recruitment period, with a subsequent follow-up period of 5 years.

Patients randomised to surgery will undergo standard surgical treatment (including SLNB and re-excision of involved margins as deemed necessary by their local multidisciplinary team), with adjuvant endocrine and radiotherapy according to local guidelines. Patients randomised to VAE will undergo the procedure under local anaesthetic, with insertion of a marker clip and post-operative mammography to assess the completeness of the excision radiologically. SLNB will not be carried out in the VAE arm of the study. Where excision is determined to be complete, patients will proceed to adjuvant radiotherapy and endocrine therapy (according to local protocols, which may include partial breast radiotherapy in keeping with NICE guidance). If residual disease is apparent on post-VAE imaging, then patients will proceed to standard surgical treatment.

In good prognosis cancers, the risk of local recurrence within the breast has been shown to be low following surgery and radiotherapy, with rates of around 1% at 5 years [25]. It is possible that this risk may be increased after VAE

due to pathological incomplete resection. However, what is critical for long-term clinical outcomes is not the presence of low-volume microscopic disease, but rather its impact on local recurrence. It is important to recognise that after surgery, a clear resection margin does not mean that there is no residual tumour in the breast. Data suggest that even where additional surgery is not carried out to clear focally involved resection margins, acceptable local recurrence rates (<3%) at 5 years can be obtained with the use of adjuvant radiotherapy and endocrine therapy [26]. Therefore, in the VAE arm of SMALL, adjuvant radiotherapy and endocrine therapy are mandated to minimise the local recurrence risk. Furthermore, local recurrence rates will be closely monitored, and not be allowed to rise above a prespecified rate (3% per year). In this setting, local recurrence is a salvageable occurrence that can be managed by further surgery and does not affect long-term survival.

SMALL includes an internal pilot phase of 18 months to determine the acceptability and feasibility of recruitment. To address potential challenges to patient recruitment (such as identifying eligible patients, differences in levels of recruiters' equipoise and patients' preference for open surgery or VAE), SMALL will employ an integrated Quintet Recruitment Intervention (QRI) [27] aimed at optimising recruitment and informed consent. The QRI uses a novel qualitative and mixed methods approach pioneered during the Health Technology Assessment Programme (HTA)-funded ProtecT study and has been shown to support recruitment to time and target in other challenging randomised trials [28].

Conclusions

The novel design of the SMALL trial provides a unique opportunity to evaluate the de-escalation of surgical treatment in screen-detected breast cancer, at a time when overtreatment remains a highly controversial issue. The introduction of VAE following a prospective randomised trial would represent a significant step forward in this setting, and it is anticipated that SMALL will pave the way for the development of future strategies for further treatment de-escalation.

Conflict of Interest

The authors declare no conflicts of interest.

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