Clinical Oncology 27 (2015) 6–8

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

The LORIS Trial: Addressing Overtreatment of Ductal Carcinoma *In Situ*

A. Francis *, L. Fallowfield †, D. Rea ‡

* *Breast Surgery Department, Nuffield House Queen Elizabeth Hospital, University Hospital Birmingham NHS Trust, Birmingham, UK*
† *Sussex Health Outcomes Research & Education in Cancer (SHORE-C), Brighton & Sussex Medical School, University of Sussex, Falmer, UK*
‡ *Clinical Trials Unit (CRCTU), School of Cancer Sciences, University of Birmingham, Birmingham, UK*

Received 11 September 2014; received in revised form 15 September 2014; accepted 29 September 2014

An unforeseen consequence of the introduction of mammographic breast screening has been the marked increase in the number of women diagnosed with ductal carcinoma *in situ* (DCIS) [1,2]. In 2009–2010, 2830 women were diagnosed with *in situ* carcinoma through the National Health Service Breast Screening Programme (NHSBSP) [3]. Screen-detected DCIS now accounts for 20% of 'cancers' identified through breast screening. However, the intent of breast screening programmes was to detect early invasive cancer, not to identify DCIS. The lengthy follow-up data now available from the NHSBSP reveal that the exponential rise in DCIS diagnoses has not been accompanied by a corresponding fall in invasive cancer incidence.

If DCIS inevitably progressed to invasive cancer then it would be a reasonable assumption that the treatment of screen-detected DCIS would result in the reduction of invasive breast cancer. Precisely the opposite has happened, with age-standardised invasive breast cancer incidence progressively rising after the introduction of screening 20 years ago. There has been a welcome levelling off in the rising incidence in the last few years, but no suggestion yet that breast cancer incidence is falling. The UK age-standardised incidence of invasive breast cancer has risen from 90.9/100 000 in 1988 to 126.2/100 000 in 2010 and DCIS from 3.6/100 000 to 16.2/100 000 in the same period [3,4]. The natural history of DCIS is not as clear as it was thought to be in the 1970s.

Analysis is confounded by a rising background incidence and multiple factors play a role, but it is far from clear that diagnosing and treating asymptomatic DCIS saves lives.

The current treatment of screen-detected but otherwise asymptomatic DCIS, leads to a diagnosis of 'cancer' and surgery for all according to stringent time targets applied to those patients with symptomatic invasive cancer. In the UK, 30% of women diagnosed with screen-detected *in situ* cancer are treated by mastectomy and 70% by breast-conservation surgery. This compares unfavourably with 26% of women with screen-detected invasive cancer who are treated by mastectomy. The management of DCIS within the National Health Service is a multidisciplinary effort consuming considerable health care resources in breast radiology, surgery, radiotherapy and out-patient follow-up.

Widely variable adjuvant treatments are offered to patients with screen-detected DCIS that are location and clinician dependant. Radiotherapy after breast-conserving surgery for screen-detected DCIS, for example, ranges from 0 to 100% in UK screening units [5].

There is little consensus among clinicians as to how DCIS should even be described [6]. Despite clinicians' best but varied efforts, women's perceptions of the risk of dying from screen-detected DCIS are the same as the risk of dying from invasive symptomatic breast cancer [7]. Furthermore, many women who attend regular mammographic screening programmes have never heard of the term DCIS and are confused by its definition and the need for treatment as if it were invasive breast cancer [8].

'Overdiagnosis' in this context refers to diagnosing healthy women with cancer who would never otherwise have presented with a symptomatic breast cancer diagnosis in their lifetime and is not confined to DCIS or the screened population. The degree of overdiagnosis of DCIS became the subject of increasingly polarised debate and growing clinical concern. The inevitable consequence of overdiagnosis is 'overtreatment' and wildly differing estimates of overtreatment published in peer-reviewed journals led to a situation where it was hard for clinicians to avoid 'those

Author for correspondence: A. Francis, Breast Surgery Department, Nuffield House Queen Elizabeth Hospital, University Hospital Birmingham NHS Trust, Edgbaston, Birmingham B15 2TH, UK. Tel: +44-121-371-5036.
E-mail address: adelefrancis@doctors.org.uk (A. Francis).

http://dx.doi.org/10.1016/j.clon.2014.09.015

twin traps of overtreatment or therapeutic nihilism' [9] and a concern that women were not being given an opportunity to make an informed choice.

The degree and intensity of public debate fired by the pronouncement by the Nordic Cochrane Group in 2010 that there is 'no convincing evidence' that the UK Breast Screening Service has saved lives and that there is 'solid evidence of serious and common harms' [10] led to the commissioning of a review of the evidence by Sir Michael Marmot and a committee of distinguished specialists. This review was welcomed by clinicians, patient representatives and users alike as a constructive attempt to resolve an issue that was not going to go away.

Their report, published in summary form and in a more detailed report [11,12], was intended to clarify the controversy and lays out the current state of knowledge with fresh point estimates for breast cancer mortality reduction and overdiagnosis. These rather predictably lie somewhere in between the extremes estimated previously for both parameters. It is very tempting to extract from this report the snappy metric that for every life saved by screening, three women will be subjected to overtreatment with its attendant physical and psychological morbidity and assume this now represents the final word on the matter. The review reminds us that there are considerable caveats to consider in the reliability of the evidence and therefore in the accuracy of their point estimates and confidence intervals. The review is a valiant attempt to estimate the effect sizes, but inevitably, as with previous incarnations using different methodologies and criteria for determining which data to include or exclude, only uses historic data.

The epidemiology of breast cancer has changed alongside technical improvements in breast radiology that result in more lesions being identified, investigated and treated than was the case in the era of the original screening trials [13]. The simple truth is that the magnitude of overtreatment today as a result of breast screening remains difficult to accurately estimate.

The Marmot Review recommended that overtreatment be addressed by research. LORIS Trial (Low Risk DCIS Trial) [14] has just opened to recruitment in the UK. This trial randomises patients with screen-detected or incidental 'low-risk' DCIS to standard treatment or active monitoring.

Accepted criteria for the adoption of a screening test include a requirement of an adequate understanding of the natural history of the condition and that treatment should be more effective if started early. Most DCIS detected is high grade and there is recognition that high-grade DCIS is more likely to progress, if untreated, to an invasive cancer, although direct evidence for this is lacking. Patients with high-grade DCIS and most patients with intermediate-grade DCIS are excluded from this trial. Recently published UK screening data [15] show the differential effect of DCIS grade on type of recurrence and time to invasive recurrence and support the model suggesting that breast cancer evolves along two distinct molecular genetic pathways [16,17], particularly as no high-grade recurrences, metastatic events or deaths were identified from the cohort of low-grade DCIS.

Participation in LORIS is open to women with asymptomatic low-grade or intermediate-grade DCIS with low-grade features (low-risk DCIS). To accommodate the recognised issue of inconsistent grading of DCIS [18], a real-time central pathology review confirms low-risk criteria and eligibility. Patients are randomised to surgery with standard adjuvant treatment and postoperative annual mammographic follow-up versus annual mammographic follow-up alone with no surgical treatment (active monitoring). The primary end point is the development of ipsilateral invasive breast cancer. The trial has a non-inferiority design aiming to show that in this group of women, active monitoring is not inferior to standard surgery. The results of the trial will allow women with screen-detected low-risk DCIS, and their clinicians, to make an informed decision regarding treatment, which is currently not possible [19].

In addition to an extensive array of secondary end points, the trial includes a comprehensive psychosocial evaluation exploring all facets of psychological well-being as well as the health economics associated with each approach.

It is recognised that the approach to patients needs to be balanced and consistent. It will be conveyed to eligible patients that the default treatment by surgery is for historical reasons, not because there is evidence for this treatment approach. Patient and public involvement were pivotal in the development of this trial. Members of the Independent Cancer Patients Voice with personal experience of treatment for breast cancer or DCIS have sat on the steering committee since its inception, supported the trial and helped to address any potential problems and concerns about acceptability to future patients. Focus groups have been held with women of screening age and their input has largely driven the content and format of the patient information documents and largely influenced the protocol. Most women at all focus groups [8] expressed an opinion that they would wish to take part in the trial if eligible. LORIS has an inbuilt feasibility study and during this time intensive work will be undertaken to assess the acceptability of the trial to patients and help multidisciplinary teams present the trial to patients in an even-handed manner.

DCIS is a heterogeneous disease with variable malignant potential and there is no question that some DCIS does indeed progress to invasive disease. The trials showing that adjuvant treatments reduce recurrent DCIS and invasive recurrences have at the same time been unable to show an effect on mortality. This is not short-term research and although annual mammography is for 10 years and the primary analysis will be carried out at 5 years, the participants will have lifelong follow-up to fully understand the natural history of low-risk DCIS and the role of surgical treatment for this condition.

Several promising molecular approaches have already been identified as potential candidates for refining patient selection for this approach [20,21] and there is a widely held expectation that ultimately this will be determined on a molecular rather than a histopathological basis. Tissue is therefore being prospectively collected from all patients to explore these and future molecular hypothesis.

The days of merely arguing about the degree of overtreatment of DCIS should be over. They have continued too long.

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