

## Overtreatment of low-grade ductal carcinoma in situ

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Commissioned commentary on "Survival Benefit of Breast Surgery for Low-Grade Ductal Carcinoma In Situ: A Population-Based Cohort Study," by Yasuaki Sagara et al. JAMA Surgery

Overtreatment of Low Grade Ductal Carcinoma In Situ (DCIS)

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DCIS comprises approximately 20-25% of all 'breast cancers' detected by mammographic screening programs. Such programs were set up to identify early invasive disease so the large numbers of all grades of DCIS diagnosed were unforeseen, unexpected and unwelcome. As the natural history of untreated DCIS is largely unknown, its management is controversial; mammogram detected DCIS is usually treated as if it is cancer, primarily with surgery. Adjuvant treatments may also be offered which vary from hospital to hospital and from country to country (1). Surgery for DCIS has remained largely unchanged since the 1970s and mastectomy is now performed more often than is seen with invasive cancer. It is 40 years since the inception of the first breast screening programs and time to question the appropriateness and the outcomes of these management policies for screen-detected DCIS.

Sagara and colleagues have scrutinized SEER data from 9 US states involving 57222 women with a median 72 months follow-up from diagnosis (2). They showed that the vast majority of patients diagnosed with all grades of DCIS who did not receive surgery did not die from breast cancer. Of those patients who received surgery, 29% had a mastectomy. Among patients diagnosed with low-grade DCIS, the weighted 10-year breast cancer-specific survival of the non-surgery group was 98.8% and for patients having surgery 98.6% ( $P = 0.95$ ). Multivariate analysis also showed no significant difference in the weighted hazard ratios of breast cancer-specific survival between the surgery and non-surgery groups for low-grade DCIS. There was also no overall survival benefit for patients with low grade DCIS who had surgery compared to those who did not.

The authors eloquently describe both the use of propensity score weighting and elucidate other potential problems in their paper such as limited information regarding patient characteristics and surgical margins etc., but flaws notwithstanding, it seems more likely than not that we have been getting the treatment of low grade DCIS wrong. Past management may have been determined with the best of intentions, but for several years now many clinicians, pathologists, statisticians and others have voiced genuine concern about the likely over-treatment of screen detected DCIS. Although independent reviews of screening programs (3) concur that overtreatment exists, statisticians and epidemiologists do not agree about its magnitude and produce varying estimates (4). This leaves women of screening age, patients and their surgeons with a dilemma that must be resolved with better prospective evidence gathered from multidimensional, comprehensive studies. This might not be easy but with more women themselves recognising the controversies surrounding DCIS (5) clinicians do need to design prospective randomised trials of active monitoring with translational

questions. This would give patients have access to a 'plan B', namely trial participation, if they are unsure about surgery.

The call by Sagara et al for a prospective clinical trial of active surveillance of low grade DCIS in the US might prove challenging, but as surgical equipoise is essential for successful trial recruitment, addressing initially the overtreatment of patients with Low Grade DCIS might be the best strategy to gain surgeons' acceptance and engagement.

A unique environment exists within the UK enabling successful recruitment to such trials. The UK clinical culture is not quite as 'risk-averse' as that in the US, and only a minority of the UK population receive screening or their medical treatment through insurance. This combination of factors permits more likelihood of enrolment in trials that offer patients 'less' treatment despite this area being recognised as a difficult one for patients and doctors alike.

The National Institute for Health Research Health Technology Assessment (NIHR, HTA) Program has recently supported the **Low Risk DCIS Study (LORIS)** <http://www.birmingham.ac.uk/loris>. This important trial, driven by clinicians in partnership with patients from Independent Cancer Patients Voice (ICPV), opened its feasibility phase in 2014. LORIS aims to enrol 932 patients with 'Low Risk' DCIS to standard treatment or active monitoring. Current recruitment is on target and shows yet again that women with 'breast cancer' are brave, well informed & altruistic.

Such trials demand thoughtful planning before funding; in LORIS, the focus groups held with women who regularly attended for mammographic screening were invaluable and showed unequivocally that they needed the facts and uncertainties associated with DCIS communicated(6). A majority welcomed an opportunity to participate in a trial addressing the issues. They highlighted the potential confusions caused by the terminology, so a survey of health care professionals was conducted to determine the best nomenclature to use in the trial when discussing DCIS (7). Finally a DVD for women considering trial entry was made; this explains the rationale and logic for the study in the even handed manner demanded for such a controversial topic and which many clinicians find challenging.

Active monitoring within LORIS requires large volume core biopsies and a real time central pathology review by expert DCIS pathologists from the UK National Sloane project to ensure that only patients with low grade features are enrolled. Further safety

features incorporate inclusion criteria designed to exclude women at higher risk of having accompanying higher grade disease, such as the absence of a mass lesion clinically and on imaging. All patients are followed up with annual mammography and appropriate Patient Reported Outcomes and health economic questions are embedded within the protocol. Pivotal to the trial is collection of tissue for translational work and both tissue and imaging banks will provide unique future resources.

The publication by Sagara and colleagues has provided an important platform on which, as they suggest, clinical trials of active monitoring can be successfully built. As the recent Time magazine headline story shows there are surgeons and patients across the US ready to address these difficult issues. Women taking part in such studies will allow future generations worldwide to make informed choices based on data that currently are unavailable.

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