Should lower risk patients with ductal carcinoma in situ be treated with adjuvant whole breast radiotherapy, after breast conservation surgery?

Jessamy Bagenal, , senior medical editor, *The Lancet*,[1] Nicola Roche, consultant breast surgeon,[1] Gill Ross, consultant clinical oncologist,[1] Anna Kirby, consultant clinical oncologist,[1] David Dodwell, consultant clinical oncologist[2]

1. The Royal Marsden Hospital, London, UK

2. Nuffield Department of Population Health, University of Oxford, Oxford, UK

Correspondence to J Bagenal jessamy.bagenal@googlemail.com

What you need to know

- Women with ductal carcinoma in situ are usually offered breast conserving surgery (BCS), often followed by whole breast radiotherapy (WBRT).
- WBRT reduces ipsilateral breast events but has not been shown [because of an absence of evidence?] to improve breast cancer specific or overall mortality.
- Patients will have different perceptions of the risks and benefits of WBRT and should be assisted in their decision making by clear presentation of the information.

Ductal carcinoma in situ (DCIS) affects around 8000 women per year in the UK.[1] Since the introduction of mammography screening, the incidence of DCIS has increased and now represents around 20% of all new screen detected breast cancers.[2]

Ductal carcinoma is categorised into low, intermediate and high grade based on histological features by a pathologist. Most cases of DCIS are treated with breast conserving surgery (BCS), often followed by whole breast radiotherapy (WBRT). An individual patient level meta-analysis (four randomised controlled trials, 3729 women) found that WBRT approximately halved the rate of ipsilateral DCIS or invasive recurrence at 10 years compared with no radiotherapy following BCS.[3] However, WBRT can cause side effects such as impaired cosmesis, skin changes, and late cardiac toxicity.[i]Patients might also find WBRT inconvenient and expensive. National Institute of Health and Care Excellence (NICE) guidelines recommend offering WBRT to all patients with DCIS.[4] The European Society of Medical Oncology guidelines suggest that WBRT might be omitted in some low risk patients.[5]

However, observational studies done in the UK, US, and Europe note wide variations in the delivery of adjuvant radiotherapy in these patients.[6] This variation possibly reflects uncertainty as to whether the benefits of WBRT are large enough to warrant blanket use of adjuvant WBRT or whether WBRT can be safely omitted in a subset of lower risk patients.

In this article we discuss the evidence surrounding radiotherapy use in DCIS.What is the evidence of uncertainty?

Search strategy
We searched the *Cochrane Library* (including the Cochrane Central Database of Controlled Trials), Ovid Medline, and clinical trial registers (clinicaltrials.gov, controlled-trials.com, who.int/trialsearch), PROSPERO, National Cancer Research Institute portfolio, Cancer Research UK, and Macmillan websites from 1990 until May 2017. We also cross referenced bibliographies. We ran multiple searches using the terms:
"Ductal carcincoma", "DCIS" AND "RADIOTHERAPY", "DCIS" AND "Treatment" in combination and alone. We selected manuscripts and trials that were most relevant to the article through discussion between the authors.

What is the risk of an ipsilateral breast event in a DCIS patient?

Evidence from three prospective studies in patients with DCIS who have undergone BCS suggests that the risk of an ipsilateral breast event continues to rise with time.[7 8 9] Studies have failed to identify a sufficiently low risk group of patients that gain no appreciable benefit in terms of reduced risk of recurrence from WBRT In a trial with 636 women with low or intermediate grade DCIS, the ipsilateral event rate was 0.9% in the WBRT arm versus 6.7% in the observation arm (hazard ratio, 0.11; 95% confidence interval, 0.03 to 0.47; P <.001).[7] A trial in 158 women with low and intermediate grade DCIS closed early as the ipsilateral breast events met the predetermined stopping rules with an ipsilateral breast event rate of 2.4% per patient-year.[8] In another trial, the risk of an ipsilateral breast event at 12 years was 14.4% for the low-intermediate grade group (561 women) and 24.6% for the high grade group (104 women).[9] Patients might have differing opinions on an acceptable rate of an ipsilateral breast event.

Scoring systems have been developed to predict the risk of local recurrence in an attempt to identify patients at low risk of recurrence who may be able to avoid WBRT and thereby guide adjuvant therapy recommendations (table 1). However, these recommendations are used variably in practice as they do not provide sufficiently precise estimates of the risk of local relapse.

Table 1 Predictive scoring systems in DCIS [Online only]

Score	Features	Validation	Analysis	Results of validation
Modified University of Southern California/Van Nuys Prognostic Index	Four clinicopathological features (age, tumour size, margin width, pathologic classification)	Prospective database validated on 706 women	Multivariate analysis to derive formula	No difference in 12 year local recurrence free survival in DCIS patients who scored as low risk on the Van Nuys Prognostic Index regardless of whether or not they were treated with WBRT

Sloane Kettering Memorial Nomogram	10 clinic-pathological, and treatment variables to estimate the probability of 10 year local recurrence (age, family history, presentation, nuclear grade, necrosis, surgical margins, number of surgeries, year of surgery, adjuvant radiotherapy, adjuvant endocrine [therapy?]) Yes	Retrospective validation on 1868 women	Multivariate Cox proportional hazards model	DCIS nomogram for prediction of 5- and 10-year ipsilateral breast event probabilities showed good calibration and discrimination, with a concordance index of 0.704 (bootstrap corrected, 0.688) and a concordance probability estimate of 0.686.
DCIS score	Genomic profile calculated from seven cancer related genes and five reference genes	327 tissue samples from registration trial designed to find a subset of DCIS patients for whom WBRT was not necessary. 718 tissue samples from established population based cohort diagnosed with DCIS and treated with BCS	Association of DCIS score analysed with risk of ipsilateral breast event using Cox regression analysis. Cox modelling used to assess relationship between independent covariates, the DCIS score, and local recurrence	The continuous DCIS score was statistically significantly associated with the risk of developing an ipsilateral breast event (hazard ratio=2.31, 95% confidence interval = 1.15 to 4.49; P=0.02) when adjusted for tamoxifen use (prespecified primary analysis) and with invasive breast events (unadjusted hazard ratio = 3.68, 95% confidence interval = 1.34 to 9.62; P = 0.01) DCIS score provided independent information on local recurrence beyond clinical pathological features

Effect of WBRT on overall or breast cancer specific mortality

Although WBRT has been shown to decrease the risk of ipsilateral local (within-breast) recurrence by around 50%, it has not been shown to improve breast cancer mortality.[11 12] The evidence from five randomised controlled trials in women with DCIS suggests that WBRT did not influence breast cancer mortality or overall survival (table 2). The individual patient-level meta-analysis reported a 10 year breast cancer mortality of around 4%.[3] so a very large study would be required to show a small reduction in breast cancer mortality from WBRT. Similarly, recent large population-based longitudinal studies find insufficient benefit of WBRT in reducing breast cancer specific mortality at 10 and 20 years to warrant its use in all patients.[12 14]

A recent study analysed 10 and 20 year breast cancer specific mortality using the Surveillance Epidemiology and End Results (SEER) data (18 registries, 108 196 women with

DCIS). Invasive recurrence increased the risk of dying from breast cancer (hazard ration 18.1, 95% confidence interval 14.0-23.6; P < 0.001), but the prevention of recurrence by WBRT did not diminish breast cancer specific mortality at 10 years.[12] It is not possible to identify and account for the potential confounding factors in a study of this type, but these results suggest that any increased mortality risk from an invasive recurrence is unlikely to be great enough to warrant WBRT.

Table 2

Another large population-based longitudinal study also used SEER data [14] to study breast cancer specific mortality after BCS alone and in patients who received BCS and WBRT. The study used a patient prognostic scoring model comprising clinical and pathological features for risk stratification and propensity scoring to address possible confounding. In this cohort of 32 144 women, breast cancer mortality rate was 0.9%. The 10 year breast cancer mortality rate was 1.8% in the WBRT group and 2.1% in the non-WBRT group (absolute difference, 0.3%; log-rank test, P= 0.003; hazard ratio, 0.73; 95% confidence interval, 0.62 to 0.88). However, the hazard ratios depicting the apparent effect of WBRT for each of the defined prognostic groups had wide confidence intervals, and a causal relationship between WBRT and reduced breast cancer mortality cannot be confirmed.

Any small benefit derived from WBRT in breast cancer specific mortality, if this exists, must be appreciated in the context that patients are more likely to die of other causes than those related to breast cancer.[14]

Is ongoing research likely to provide relevant evidence?

We searched clinical trial registries and found three large studies that might shed light on some of the uncertainty around the use of radiotherapy in patients with DCIS. The two largest trials aim to identify low risk DCIS patients based on clinical and pathological factors and compare active surveillance with standard therapy (breast conserving surgery and WBRT) using 10 year rate of invasive local recurrence as an endpoint[15] (table 3). The smaller “Forget me not” cohort is part of a larger database and will report outcomes for women who did not have surgery for DCIS These studies should help to elucidate the natural history of DCIS and how to identify patients with a low risk of invasive recurrence.

Table 3 New trials

Trial name	Location	Design	Population	Intervention	Comparator	Outcome	Expected results
Low	International	Prospective	1240 women	Active	Standard	10 year	2029

risk DCIS LORD	, multicentre	open label randomised phase III non-inferiority trial	>45 with screen detected asymptomatic pure low grade DCIS on vacuum biopsy	surveillance	treatment for DCIS	ipsilateral breast cancer free percentage	
Low risk DCIS Trial LORIS	Multi centre UK based	Prospective randomised controlled phase III non inferiority trial	932 >46 screen detected asymptomatic pure non-high grade DCIS	Active surveillance	Surgery	10 year ipsilateral invasive breast cancer free survival time	2024
Forget me not	Multicentre, UK based	Retrospective cohort	DCIS patients not treated with surgery or who underwent significant [Looks incomplete. What does this mean?] (over 12 months) in surgical treatment				Results released at time of publication [Can these be included if relevant?]

What to do in the light of the uncertainty?

The benefit of WBRT in many cases is small, and patients who wish to avoid WBRT can be supported and reassured in this decision. Discuss the uncertainty over the risks and benefits of WBRT treatment with patients fully. It is likely that a subset of patients does not need WBRT, but we have yet to develop the best way to identify this group.[5] A reasonable approach is to risk stratify patients using one of the scoring systems in table 1. Table 4 lists clinical and pathological features shown to be associated with recurrence. Where possible, use shared decision making aids to help the conversation with patients.[16] Offer counselling with specialist nurses and provide information leaflets that display all treatment options.

Table 4 Clinical pathological features found to be associated with recurrence

Feature	Evidence
Young age	High quality: analysis from one randomised trial and large well conducted observational studies[17 18 19]
Symptomatic presentation	High quality: analysis from two randomised trials[1 20]
Family history	Low quality: small retrospective cohort study[21]
Multifocality	High/moderate quality: large retrospective cohort studies[22] and central pathology review of patients entered into randomised trial[23]

Size	High/moderate quality: large retrospective cohort studies[24] and central pathology review of patients entered into randomised trial[23]
Margin status	High quality: analysis from three randomised trials and retrospective study of pathological samples[1 25 26]
Volume of disease at closest margin	Moderate quality – one retrospective cohort study[27]
Nuclear grade	High quality: analysis from randomised trial[1] and case cohort study within a randomised trial[28]
Presence of comedo necrosis	High quality: analysis from randomised trial[29] case cohort study within a randomised trial[28] and and central pathology review of patients entered into randomised trial[7]
Architectural pattern	High quality: analysis from randomised trial[1] and central pathology review of patients entered into randomised trial[23]

What patients need to know?

- Ductal carcinoma in situ very rarely leads to death.
- Most DCIS is treated with breast conserving surgery (BCS), often followed by whole breast radiotherapy (WBRT).
- WBRT reduces the risk of recurrence, but WBRT does not reduce the risk of dying from breast cancer or improve overall survival.
- You should expect your doctor to advise you on the likely benefits and risks of radiotherapy, taking into consideration the severity of your disease, and accepting that there is some uncertainty about the benefits of treatment.
- Because of this uncertainty, you might wish to explore what type of treatment is best for you based on your personal risk tolerance and life expectancy.

Recommendations for future research

- Development of better predictive markers/tools to identify a group of patients in whom WBRT can be safely omitted
- Explore how current evidence is understood by clinicians and delivered to patients to reduce geographical variations in the proportion of patients being offered WBRT
- Explore how patients feel about making decisions around WBRT

Education into Practice

How has reading this article changed the way you might approach discussions of radiotherapy with patients with DCIS?

How might you better support patients who have received a diagnosis of DCIS?

How patients were involved in the creation of this article

A draft manuscript was reviewed by representatives of ICPV. They were happy with the overall manuscript but had specific statements about what a patient can expect from their doctor and this was addressed in the what patients need to know box.. A patient with DCIS kindly reviewed this paper. She endorsed the uncertainty around appropriate treatment for DCIS and that medical professionals must recognise that patients have different personal risk tolerances. We have emphasised this and suggest that doctors discuss the risk and benefits of WBRT and assist patients in making a shared decision.

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