Molecular phenotypes of DCIS predict overall and invasive recurrence†

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Background: Molecular phenotypes of invasive breast cancer predict early recurrence. Ductal carcinoma in situ (DCIS) exhibits similar phenotypes, but their frequency and significance remain unclear. To determine whether DCIS molecular phenotypes predict recurrence, 314 women (median age 57.7 years) with primary DCIS who were screened or entered DCIS trials in a specialist breast unit from 1990 to 2010 were studied.

Patients and methods: Expression of Ki67, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) within primary DCIS was established using immunohistochemistry (IHC). Patients were subdivided into molecular phenotypes using IHC surrogates [Luminal A (ER/PR+/HER2−), Luminal B (ER/PR+/HER2+), HER2 type (ER and PR−/HER2+) or triple negative (ER/PR/HER2)] and recurrence rates compared.

Results: Overall, there were 57 (18.2%) recurrences, 35 (11.2%) DCIS and 22 (7%) invasive cancer. A low rate of recurrence at 5 years was seen in Luminal A DCIS (7.6%), compared with 15.8%–36.1% in other phenotypes. Independent predictors of overall recurrence on multivariate analysis were involved (<1 mm) surgical margins (HR 4.31, P < 0.001), high-grade lesions (HR 2.28, P < 0.024) and molecular phenotype (HR 5.14, P = 0.001 for Luminal B; HR 6.46, P < 0.001 for HER2 type and HR 3.27, P = 0.028 for triple-negative disease compared with Luminal A DCIS). Independent predictors for invasive recurrence were high Ki67 expression (HR 1.04, P = 0.021) and molecular phenotype (HR 13.4, P = 0.014 for Luminal B; HR 11.4, P = 0.027 for HER2 type and HR 10.3, P = 0.031 for triple negative compared with Luminal A DCIS).

Conclusions: DCIS molecular phenotype predicts for both overall and invasive recurrence. HER2 testing of DCIS could help clinicians individualise the treatment of patients with DCIS.

Key words: molecular phenotype, DCIS, recurrence, Luminal A

introduction

Ductal carcinoma in situ (DCIS) comprises around 20% of all screening detected breast malignancies in the UK. Its management remains controversial; the natural history remains unclear. As DCIS is a non-obligatory precursor of invasive cancer, some women currently receive radical treatment of a condition that left untreated would have remained harmless. If no treatment is offered, some 14%–46% of patients with DCIS will progress to invasive cancer within 10 years [1–3]. The challenge is to accurately predict patients most at risk of disease progression to target appropriate treatment at this subset, allowing the lowest risk to avoid overtreatment.

Prospective randomised trials have moulded the use of adjuvant therapies following breast-conserving surgery (BCS) in DCIS; none of which have shown any reduction in breast cancer mortality, which remains 1%–2% after 10 years [4–6]. Adjuvant radiotherapy was evaluated in the NSABP (National Surgical Adjuvant Breast and Bowel Project)-B17 [4], EORTC (European Organisation for Research and Treatment of Cancer) 10 853 [5] and UK/ANZ [6] trials. A meta-analysis demonstrated an overall 52% reduction in local recurrence after adjuvant radiotherapy, although 12%–20% of DCIS lesions still recurred by 10 years [7]. These trials were not designed to identify high-/low-risk patients, and no subgroup of patients has been identified in which radiotherapy can be avoided. However, in the UK and USA, ~50% of patients with large, high-grade tumours receive
radiotherapy; younger women more likely to receive treatment [8, 9].

In the NSABP B-24 and UK/ANZ DCIS trials, tamoxifen failed to show overall survival benefit. The NSABP B-24 trial reported decreased invasive recurrence from 7% to 4% after 5 years of tamoxifen treatment. Pre-menopausal women <50 years old showed the greatest benefit [10]. The UK/ANZ DCIS trial failed to show a significant effect on ipsilateral invasive disease (HR 0.95, CI 0.66–1.38, P = 0.8), but showed a decrease in recurrent ipsilateral DCIS (HR 0.7, CI 0.51–0.86, P = 0.003) and contralateral tumours (HR 0.44, CI 0.25–0.77, P = 0.005) after a median follow-up of 12.7 years [11]. Neither trial prospectively determined estrogen receptor (ER) status. About 30% of women had involved excision margins. On retrospective review of the B-24 pathology slides, patients with ER+ disease were most likely to benefit from tamoxifen treatment [7]. The true benefit of tamoxifen in DCIS treatment may therefore have been underestimated.

Patients who undergo mastectomy for DCIS have a low recurrence rate of around 1%–5% after 10 years, although recurrence tends to be invasive. The preferred operation for patients with localised DCIS is BCS, after which around 25% of patients recur within 10 years, 50% of which is invasive [7, 12]. Randomised trials have identified that close (<1 mm) or involved margins at the time of surgery, younger age at diagnosis (<40 years), high-grade disease and comedo necrosis are risk factors for recurrence post-BCS [5, 7–11].

Prediction of recurrence risk and treatment of invasive cancer are tailored through the use of molecular markers, e.g. HER2 status and ER status. The only molecular marker in routine clinical use in the management of DCIS in the UK is the ER; ER-negative tumours are more likely to recur [12–14]. The human epidermal growth factor receptor 2 (HER2) is inversely related to ER receptor status in DCIS [15, 16], but its prognostic significance remains controversial. In a systematic review, evaluating the prognostic value of HER2 status in DCIS, HER2 overexpression was an independent prognostic indicator for recurrence in 3 of 15 studies [17]. Ki67 is a nuclear protein used as a proliferation marker and a strong prognostic indicator for poorer outcome in early, node-negative invasive breast cancer. Although a higher percentage of Ki67-positive cells correlates with ER negativity in DCIS [15], higher percentage expression alone has failed to predict early recurrence previously [15, 18]. Kerlikowske et al. combined Ki67, ER and HER2 expression data to show that patients with ER-DCIS with high levels of Ki67 (>10%) that are HER2-positive have a greater risk of developing a local recurrence than other groups [13].

Gene expression profiling and hierarchical cluster analysis have been used to divide patients with invasive cancer into at least four different molecular phenotypes [19]. These phenotypes can be applied prognostically to help direct appropriate adjuvant therapy [20]. The cost of gene expression profiling has limited clinical use, but several research groups have shown that immunohistochemical staining can be used as a surrogate marker for gene expression profiling in invasive breast cancer, utilising ER, progesterone receptor (PR) and HER2 protein expression to split the patients into four different molecular phenotypes [20, 21]; Luminal A (ER/PR+ and HER2−), Luminal B (ER+/PR+ and HER2+), HER2 type (ER/PR− and HER2+) and triple negative (ER/PR− and HER2−). Similar subtypes have been found in DCIS tumours using IHC [22, 23]. The prognostic significance of grouping DCIS into these subtypes is not yet known.

Recently, the Genomic Health DCIS assay has indicated a group of patients with a low risk of breast recurrence after surgery, in the absence of radiotherapy and a group with a high risk (up to 30%) of local recurrence at 7 years [24]. Thus, it may be possible to stratify for treatment on the basis of individual expression of receptors or genes in DCIS.

The aim of this study was to confirm the frequency of molecular phenotypes, in a cohort of patients treated with pure DCIS of the breast, using IHC surrogate markers to ascertain whether the molecular phenotypes present could be identified and used to predict disease recurrence accurately.

### Table 1. Tumour and patient characteristics by molecular phenotype

<table>
<thead>
<tr>
<th></th>
<th>Luminal A (ER or PR+ HER2−) [N = 134]</th>
<th>Luminal B (ER or PR+ HER2+) [N = 88]</th>
<th>HER2 type (ER and PR− HER2+) [N = 51]</th>
<th>Triple negative (ER and PR− HER2−) [N = 41]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td></td>
</tr>
<tr>
<td>Tumour size (mm)</td>
<td>15.8 (1, 100)</td>
<td>20.0 (2, 130)</td>
<td>24.5 (5, 90)</td>
<td>15.0 (5, 120)</td>
<td>0.005*</td>
</tr>
<tr>
<td>High-grade number (%)</td>
<td>63 (48%)</td>
<td>64 (74%)</td>
<td>42 (82%)</td>
<td>33 (80%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ki67 (%)</td>
<td>13.5 (0.5, 40.7)</td>
<td>16.1 (2.0, 61.1)</td>
<td>20.2 (7.0, 47.2)</td>
<td>17.7 (3.4, 33.4)</td>
<td>0.042*</td>
</tr>
<tr>
<td>Microinvasion present</td>
<td>11 (9%)</td>
<td>7 (9%)</td>
<td>7 (14%)</td>
<td>1 (3%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Surgery type Mx (versus BCS)</td>
<td>31 (23%)</td>
<td>35 (40%)</td>
<td>28 (55%)</td>
<td>13 (32%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Margin status involved (&lt;1 mm</td>
<td>9 (7%)</td>
<td>9 (10%)</td>
<td>9 (18%)</td>
<td>3 (8%)</td>
<td>=0.14</td>
</tr>
</tbody>
</table>

Tumour size: HER2 type > Luminal A; high grade: Luminal A < Luminal B, HER2 type, triple negative; Ki67%; HER2 type > Luminal A; Surgery type (Mx): HER2 type > Luminal A.

*Indicates that the values are statistically significant.
methods

patients
In total, 314 patients presenting with primary, pure DCIS who were screened for, or entered, five DCIS clinical trials in one breast unit (DCIS I [8], IBIS II (DCIS) [25] [both adjuvant trials], IRESSA trial, ERISAC [26] and lapatinib DCIS [all preoperative window trials requiring ER and HER2 screening]). All trials were peer-reviewed with ethical approval.
Patients consented for their data to be recorded confidentially, and initial diagnosis and follow-up clinic–pathological data to be used which included ER, PR and HER2 expression and Ki67.

pathological data and immunohistochemistry
The types of DCIS, size, grade and margin status were assessed according to NHSBSP Quality Assurance standards [27] and prospectively recorded on all patients. Methods for ER, PR, HER2 and Ki67 have been previously described [26, 28]. Immunostaining was nuclear for Ki67, ER and PR and predominantly cell membranous for HER2 with a cytoplasmic component. For each section, a minimum of 1000 cells were scored across randomly selected areas of DCIS at a magnification of ×400 using a grid graticule cell counter. Ki67, ER and PR scores were calculated as a percentage of positively stained nuclei (i.e. positive cells/total number of cells × 100%). ER and PR positivity was defined as >5% stained nuclei, according to a scoring system and after two scorers had assessed the DCIS. HER2 staining was scored as 0 (absent) to 3 (maximum cytomembranous staining seen, compared with invasive cancer control), with a score of >2 considered HER2-positive. Tumours were classified as high Ki67 (≥14% staining) or low (<14%) as defined by previous research groups [13, 14].

statistical analysis
Patients were subdivided into molecular phenotype subgroup according to ER, PR and HER2 status. The simple $\chi^2$ test, one-factor ANOVA or the Kruskal–Wallis test, as appropriate, was used to compare the distribution of tumour and patient characteristics between groups.
Univariable Cox proportional hazards regression analyses were carried out to assess the relationship between predictive factors and overall and invasive disease-free survival. Recurrence time was measured from time of surgery to time of recurrence or 1st May 2013. Kaplan–Meier-derived 5- and 10-year recurrence rates were also calculated. Simple log-rank tests were used to compare disease-free survival by molecular phenotype. All analyses used the conventional two-sided 5% significance level.

power calculation
With 57 recurrences in all (of which, 22 were invasive recurrences), the study will have 80% power to detect hazard ratios relating to categorical predictors for overall recurrence of 2.1 or more and to detect hazard ratios of 3.2 or more for invasive recurrence (nQuery Advisor, version 7.0).

results
Mean age for all patients was 57.7 years (range 29–82 years). The majority of patients had high-grade (64.3%) and ER-positive...
(70.7%) DCIS, with a mean diameter of 24 mm (1–130 mm). One hundred and thirty-nine tumours (44.3%) overexpressed HER2. BCS was the surgical treatment of 207 (65.9%) patients. Fifty-seven patients (18.2%) recurred within a median follow-up time of 60.5 months (12–240 months): 35 recurrent DCIS (11.1%) and 22 (7%) with invasive disease. Using the IHC surrogates of ER, PR and HER2, the DCIS was divided into four phenotype groups (Table 1). Analysis revealed that the different phenotypes were well matched according to age at diagnosis and size of tumour (Table 1). The majority of the patients had Luminal A disease [134 patients (42.7%)], which was treated with BCS [103 patients (76.9%)]. These tumours had the lowest risk of overall recurrence at 10 years (7.6%) (Table 2). Whereas only 48% of Luminal A tumours were high grade, 74% of Luminal B, 82% of HER2 type and 80% of triple-negative tumours were high grade ($P < 0.001$). Mean percentage of Ki67 expression was lower in the Luminal A group (13.5%), compared with the other molecular phenotypes (Luminal B 16.1%, HER2 type 20.2% and triple negative 17.7%; Table 1). Differences in the four phenotypes were reflected in differing recurrence rates. The lowest overall recurrence was seen in the Luminal A group with only 7.6% of cases recurring, compared with 23.2% Luminal B, 36.1% HER2 type and 15.8% triple-negative tumours after 5 years of follow-up (Table 2; $P < 0.001$). Invasive recurrence rates differed between phenotypes; 1.3% of Luminal A cases had an invasive recurrence, compared with 16.1% Luminal B, 29.5% HER2 type and 23.1% of triple-negative cases at 10-year follow-up ($P = 0.004$; Table 2).

**surgical management and adjuvant therapy**

There were no differences in adjuvant radiotherapy after BCS between molecular phenotypes (17.5% Luminal A, 18.9% Luminal B, 17.4% HER2 type, 14.3% triple-negative tumours, $P = 0.96$) or adjuvant endocrine therapy in ER-positive cases (12.8% of patients with Luminal A tumours and 11.4% with Luminal B tumours, $P = 0.09$). Non-Luminal A phenotypes were more likely to undergo mastectomy, explained by the fact that Luminal A tumours had a smaller mean diameter compared with other phenotypes ($P = 0.005$; Table 1).

**predictors of overall disease recurrence on univariate analysis**

Patients undergoing mastectomy were less likely to suffer a disease recurrence than those undergoing BCS (HR 0.45, 95% CI 0.23–0.86; $P = 0.017$). Thirty patients had involved surgical excision margins (<1 mm). This predicted for disease recurrence (HR 5.43, 95% CI 3.1–9.5; $P < 0.001$). These patients were treated for DCIS before 2000. More recently, departmental standards have ensured that patients with close margins are offered re-excision.

Biological characteristics that predicted overall recurrence were high-grade disease compared with low-grade (HR 2.56, 95% CI 1.32–4.96; $P = 0.005$) and high %Ki67 expression (>14%) compared with low expression (HR 1.03, 95% CI 1.01–1.05; $P = 0.019$). Age at diagnosis, the presence/absence of comedo necrosis and the type or size of the tumour all failed to predict for disease recurrence on univariate cox regression analyses (Table 3, unadjusted model data).

The molecular phenotype of DCIS also predicted for overall disease recurrence. The HER2 phenotype predicted a highest risk of recurrence compared with Luminal A disease (HR 6.72, 95% CI 2.76–16.4; $P < 0.001$), followed by the Luminal B phenotype (HR 5.52, 95% CI 2.38–12.8; $P = 0.001$). The triple-negative
phenotype was the smallest group in this patient cohort (41 patients), but still had a higher overall disease recurrence risk compared with Luminal A disease (HR 3.82, 95% CI 1.45–10.0; \( P = 0.007 \)).

The recurrent disease, whether invasive or in situ, expressed the same molecular phenotype as the original DCIS in 83% of cases.

**independent prognostic indicators of overall disease recurrence after multivariate analysis**

Surgery type (BCS versus mastectomy), involved surgical margins, high-grade disease and tumour molecular phenotype compared with luminal A disease all remained independent predictors for overall disease recurrence on multivariate analysis (Table 3, adjusted model data). The Kaplan–Meier survival curves showing time to overall disease recurrence for the molecular phenotypes are shown in Figure 1A.

**predictors of invasive recurrence**

Invasive recurrence is particularly important, as patients have a potentially increased risk of breast cancer mortality. Significant predictors of invasive recurrence on univariate analysis were high Ki67 expression (>14%; HR 1.05, 95% CI 1.01–1.09; \( P = 0.021 \)) and molecular phenotype, compared with Luminal A disease (HR 14.5, 95% CI 1.83–114; \( P = 0.011 \) for Luminal B, HR 17.8, 95% CI 2.14–148; \( P = 0.008 \) for HER2 type and HR 15.7, 95% CI 1.89–130; \( P = 0.011 \) for triple-negative disease; Table 4, unadjusted data). Both Ki67 expression and molecular phenotype remain independent predictors of recurrence on multivariate analysis with minimal adjustment to hazard ratios (Table 4, adjusted model data).

The Kaplan–Meier survival curves for time to invasive disease recurrence are shown in Figure 1B.

### Table 4. Predictors for invasive recurrence using the Cox proportional hazards model

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unadjusted model HR (95% CI)</th>
<th>( P )-value</th>
<th>Adjusted* model HR (95% CI)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>0.96 (0.91, 1.01)</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour size (versus &lt;15 mm)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>15–25 mm</td>
<td>1.07 (0.41, 2.78)</td>
<td>0.89</td>
<td></td>
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<tr>
<td>&gt;25 mm</td>
<td>0.40 (0.11, 1.47)</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High grade (versus lower grade)</td>
<td>1.72 (0.67, 4.41)</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ki67 (per %)(^b)</td>
<td>1.05 (1.01, 1.09)</td>
<td>0.008*</td>
<td>1.04 (1.01, 1.08)</td>
<td>0.021*</td>
</tr>
<tr>
<td>Microinvasion present (versus absent)</td>
<td>1.08 (0.25, 4.70)</td>
<td>0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery type Mx (versus BCS)</td>
<td>0.86 (0.35, 2.11)</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Margin status involved (versus clear)</td>
<td>2.41 (0.81, 7.17)</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular phenotype (versus Luminal A)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal B</td>
<td>14.5 (1.83, 114)</td>
<td>0.011*</td>
<td>13.4 (1.70, 106)</td>
<td>0.014*</td>
</tr>
<tr>
<td>HER2 type</td>
<td>17.8 (2.14, 148)</td>
<td>0.008*</td>
<td>11.4 (1.31, 99)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Triple negative</td>
<td>15.7 (1.89, 130)</td>
<td>0.011*</td>
<td>10.3 (1.24, 86)</td>
<td>0.031*</td>
</tr>
</tbody>
</table>

When analysing the whole patient cohort, i.e. excluding Ki67 from the multivariate analysis, only molecular phenotype showed a significant independent relationship with invasive recurrence.

*Based on \( n = 175 \) patients and adjusted for Ki67% and molecular phenotype.

\(^b\)Based on data from 175 patients only (64 Luminal A, 50 Luminal B, 27 HER2 and 34 triple negative).

*Indicates that the values are statistically significant.

**discussion**

DCIS is a heterogeneous disease, with molecular phenotypes seen in invasive cancer presenting in primary DCIS using IHC surrogate markers. These molecular phenotypes can be used to independently predict for both overall and, importantly, invasive recurrence. DCIS subtypes have the potential to identify women more likely to develop disease recurrence following surgery and will benefit from maximal adjuvant therapy, compared with those with ER+, HER2– (Luminal A) lesions, who could potentially avoid adjuvant treatment.

Patients who undergo BCS are more likely to suffer a disease recurrence compared with mastectomy patients. Those with involved surgical margins are at highest risk [8, 12, 29]. The optimal radial surgical margin width in DCIS remains controversial in the literature. Our unit guidelines (changed in 1997) suggest that a radial margin \( \geq 1 \) mm is acceptable, based on previously published data [25].

Before 2000, we did not use radiotherapy if margins were clear by \( \geq 1 \) mm or in small tumours <2 cm in size, and thus radiotherapy use was under 18% overall. The low recurrence rate, particularly in the Luminal A ER-positive/HER2-negative DCIS, reflects a low risk of recurrence in the absence of radiotherapy and indicates a difference in the molecular phenotypes with regard to recurrence and radiotherapy sensitivity. Although this is non-randomised data, the long follow-up and the fact that the other non-Luminal A subtypes recurred within 5 years indicate this is a genuine finding.

We found that patients diagnosed with high-grade tumours were more likely to recur than intermediate or low-grade tumours (HR 2.28, 0.024); however, the presence of comedo necrosis within the tumour failed to predict for recurrence. Patient age was not an independent predictor of recurrence, but the...
dataset used for analysis lacks patients of a younger age, as the majority of DCIS lesions are diagnosed only on screening mammogram and UK screening did not commence until patients were 50 years old.

High Ki67 expression (>14%) was an independent predictor for invasive recurrence in DCIS, whereas previous studies have failed to show the predictive value of Ki67 in DCIS. Previous studies have only investigated overall recurrence and have not looked specifically at invasive recurrence alone. Kerlikowske et al. combined Ki67 with ER and HER2 expression data to show that patients with ER-negative DCIS express high levels of Ki67 (>10%) and HER2-positive had a greater risk of developing a local DCIS recurrence than other patient groups, which accords with our findings.

The molecular phenotype of DCIS is an independent predictor for both overall and, more importantly, invasive recurrence, when compared with the Luminal A group. Molecular phenotypes do exist in DCIS, but previous studies did not examine the relationship between receptor expression and overall or invasive recurrence. Gene signatures have yet to provide prognostic information for DCIS tumours, although an OncotypeDX for DCIS is currently being validated. Determination of molecular phenotypes of DCIS using surrogate immunohistochemical markers is an economically viable approach to aid identification of women at high risk of recurrence. ER-negative/HER2-positive patients need maximal adjuvant treatment to avoid invasive recurrence. In contrast, lower risk ER-positive/HER2-negative patients whose invasive relapse is significantly less could potentially avoid overtreatment with radiotherapy. The HER2 status of pure DCIS is not currently routinely measured in clinical practice in the UK, but clinicians should consider routine assessment of HER2 status for DCIS as well as invasive breast cancer.

ethics committee approval
All trials received ethics committee approval and patients screened or entered agreed to their data being used for follow-up studies.

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disclosure
The authors have declared no conflicts of interest.

references
Long-term effects of inhaled budesonide on screening-detected lung nodules

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Background: A previously carried out randomized phase IIb, placebo-controlled trial of 1 year of inhaled budesonide, which was nested in a lung cancer screening study, showed that non-solid and partially solid lung nodules detected by low-dose computed tomography (LDCT), and not immediately suspicious for lung cancer, tended to regress. Because some of these nodules may be slow-growing adenocarcinoma precursors, we evaluated long-term outcomes (after stopping the 1-year intervention) by annual LDCT.

Patients and methods: We analyzed the evolution of target and non-target trial nodules detected by LDCT in the budesonide and placebo arms up to 5 years after randomization. The numbers and characteristics of lung cancers diagnosed during follow-up were also analyzed.

Results: The mean maximum diameter of non-solid nodules reduced significantly (from 5.03 mm at baseline to 2.61 mm after 5 years) in the budesonide arm; there was no significant size change in the placebo arm. The mean diameter of partially solid lesions also decreased significantly, but only by 0.69 mm. The size of solid nodules did not change. Neither the number of new lesions nor the number of lung cancers differed in the two arms.

Conclusions: Inhaled budesonide given for 1 year significantly decreased the size of non-solid nodules detected by screening LDCT after 5 years. This is of potential importance since some of these nodules may progress slowly to adenocarcinoma. However, further studies are required to assess clinical implications.

Clinical trial number: NCT01540552.

Key words: budesonide, lung cancer, chemoprevention, low-dose computed tomography, screening

introduction

Low-dose computed tomography (LDCT) is effective for the early detection of lung cancer in high-risk populations: it identifies early stage lung cancers with high sensitivity, and reduces lung cancer mortality [1, 2]. LDCT also identifies numerous indeterminate lung nodules, some of which may be preinvasive or early invasive cancers, and require investigation. In particular, CT-detected non-solid nodules are the category of nodules most likely to represent precursors of adenocarcinoma. Kim et al. [3] reported that around 80% of persistent non-solid nodules proved to be premalignant or minimally invasive adenocarcinoma.

To assess the effect of budesonide—a glucocorticoid and potential chemopreventive [4]—on CT-detected nodules, we carried out a randomized, double-blind, phase IIb trial.