Meta-analysis

Meta-analysis of sentinel node biopsy in ductal carcinoma *in situ* of the breast

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Background: **The need for sentinel lymph node (SLN) biopsy in patients with a preoperative diagnosis of ductal carcinoma *in situ* (DCIS) is debated. Advocates recommend such biopsy based on a high incidence of SLN involvement in some series. Opponents discourage SLN biopsy based on a perceived low incidence of nodal involvement in this setting. These contradictory arguments are generally based on small studies. The present study is a meta-analysis of the reported data on the incidence of SLN metastasis in patients with DCIS.**

Methods: **A search of electronic databases identified studies reporting the frequency of SLN metastases in DCIS. The random-effects method was used to combine data.**

Results: **Twenty-two published series were included in the meta-analysis. The estimate for the incidence of SLN metastases in patients with a preoperative diagnosis of DCIS was 7·4 (95 per cent confidence interval (c.i.) 6·2 to 8·9) per cent compared with 3·7 (95 per cent c.i. 2·8 to 4·8) per cent in patients with a definitive (postoperative) diagnosis of DCIS alone. This was a significant difference with an odds ratio of 2·11 (95 per cent c.i. 1·15 to 2·93).**

Conclusion: **Patients with a preoperative diagnosis of DCIS should be considered for SLN biopsy.**

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Introduction

Ductal carcinoma *in situ* (DCIS) is detected in approximately 2800 patients each year by the National Health Service Breast Screening Programme (NHSBSP) in the UK[1]. In the USA, over 50 000 women were diagnosed with DCIS in 2006[2]. DCIS accounts for 18 per cent of all newly diagnosed breast cancers in the USA and comprises approximately 20 per cent of all breast carcinomas detected by the NHSBSP[2,3]. At present the treatment of DCIS comprises wide local excision or mastectomy, depending on the extent of disease. Radiotherapy may be indicated for patients treated with breast conservation, to reduce the risk of local recurrence[4,5]. Only 2 per cent of patients with DCIS alone are expected to die from breast cancer[6,7]. The status of the regional lymph nodes is the most important prognostic factor and predictor of survival in breast cancer, and has important implications in treatment decisions, including determining the choice of adjuvant therapy. Removing axillary nodes containing metastases is also of therapeutic value. Most patients with lymph node metastases subsequently receive adjuvant therapy including radiotherapy, endocrine therapy and/or chemotherapy[8].

The management of the axilla in DCIS has changed dramatically over the years[9]. By definition, DCIS is preinvasive and does not have the potential to spread to regional lymph nodes. Axillary dissection for DCIS, practised in the 1980s, was gradually abandoned through the 1990s and further follow-up showed that its omission in patients with pure *in situ* disease had no adverse effect on survival or recurrence[9–15]. Most patients with DCIS and lymph node metastases probably harboured an unrecognized focus of invasion in the breast or had metastases subsequent to an invasive local recurrence[16].

The advent of sentinel lymph node (SLN) biopsy, with its low morbidity[17], prompted interest in its use in patients with DCIS who were considered to be at high risk of harbouring an invasive component, such as those with

adverse clinical or histological features (large, palpable tumours, mammographic mass, high grade). With the more detailed histopathological examination afforded by SLN biopsy, including an increase in sampling volume/serial sectioning and immunohistochemistry, higher nodal involvement frequencies of up to 13 per cent were reported in patients with DCIS[18,19]. As a result, some authors recommended that SLN biopsy should be performed in all patients with a preoperative core biopsy diagnosis of DCIS. However, subsequent studies found a lower rate of nodal involvement which discouraged routine SLN biopsy[20–23]. Most of these studies were small retrospective series. To date there has been no prospective randomized trial to address the value of SLN biopsy in patients with DCIS.

Methods

The process of identifying eligible studies is summarized in *Fig. 1*. A literature search of electronic databases, including Medline, Embase, CINHAL, Ovid and The Cochrane Library, up to August 2007 was conducted. The following search terms were used: ductal carcinoma *in situ*, intraductal carcinoma, DCIS, combined with sentinel node, sentinel lymph node biopsy, axillary lymph node, sentinel node mapping, axillary surgery and axillary dissection. The 'related articles' command was used to broaden the search. No language restrictions were applied during the search. References cited in the identified articles were searched for additional studies. Some studies of SLN biopsy in DCIS assess the sentinel node biopsy-positive frequency in patients with a definitive (postoperative) diagnosis of DCIS, whereas others report this frequency in patients using the preoperative initial core biopsy diagnosis of DCIS. Given that 10–30 per cent of patients with a preoperative core biopsy diagnosis of DCIS will eventually turn out to harbour invasive cancers[24–27], the frequency of SLN metastatic involvement in these two patient groups may be different. Therefore, a meta-analysis of these two different sets of publications was performed separately.

Data on number of patients, SLN biopsy technique, number of patients with involved SLNs, type of histological examination, and preoperative and postoperative histology were extracted, tabulated and analysed. Log-odds transformation of the incidences of positive SLNs was used in performing the meta-analysis. Continuity correction was applied to studies with zero counts (no positive SLNs) and these were given an arbitrary small count of 0·5 to avoid computational problems. The Q statistic (χ^2) for the between-study heterogeneity of the log-odds was obtained. The DerSimonian–Laird random-effects model was used for the meta-analysis. The pooled proportion was estimated along with the corresponding 95 per cent confidence intervals (c.i.). Forest plots were produced using R statistical software (R Foundation for Statistical Computing, Vienna, Austria). $P < 0{\cdot}050$ was considered significant. The difference between the frequency of SLN metastatic involvement in the two populations was evaluated by dividing the difference in pooled log-odds, using the standard error of the difference, and comparing the result with the standard normal distribution.

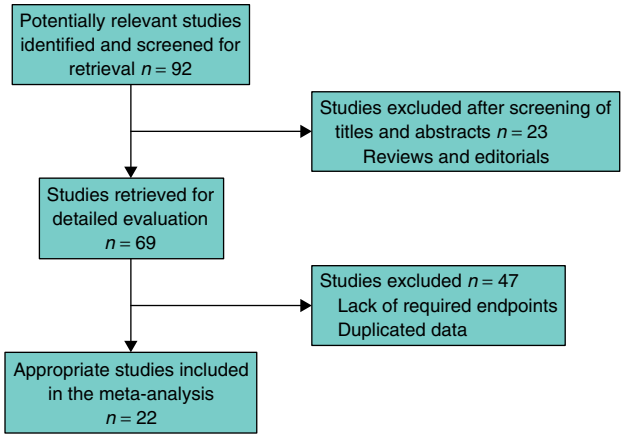

Fig. 1 Flow chart for selection of studies for the meta-analysis

Results

The titles and abstracts of the retrieved publications were reviewed. Articles that reported percentage SLN positivity in patients with a diagnosis of DCIS were reviewed in detail and their data included in the meta-analysis. Publications that had not reported percentage SLN positivity data, review articles and editorials were excluded from the meta-analysis. One study was excluded because an update of the data from the same group, published more recently, was used instead[18,28]. Twenty-two publications reporting SLN biopsy results in patients with the diagnosis of DCIS were included in the meta-analysis. The combined study population was 3166 patients. The reasons for SLN biopsy were not detailed in many of these studies. As such biopsy is not routine practice in DCIS, most of the patients who had been selected for biopsy were believed to be at high risk of harbouring occult invasive disease[29,30]. Therefore, the population of patients who were considered for SLN biopsy was probably homogeneous with similar high-risk characteristics.

The reported incidence of SLN metastatic involvement varies in these relatively small series. Studies that assessed the frequency of SLN positivity in patients with a preoperative diagnosis of DCIS reported values from 0

to 16·7 per cent (*Table 1*). The test for heterogeneity suggested that these 11 studies were not significantly heterogeneous ($\chi^2 = 16{\cdot}07$, 10 d.f., $P = 0{\cdot}098$). A meta-analysis of the data on SLN positivity from these studies gave an overall positivity frequency of 7·4 (95 per cent c.i. 6·2 to 8·9) per cent (*Fig. 2*). There was significant between-study heterogeneity in the 11 studies of patients with a definitive (postoperative) diagnosis of DCIS ($\chi^2 = 27{\cdot}82$, 10 d.f., $P = 0{\cdot}002$). A meta-analysis of the data on SLN positivity from these studies yielded an overall positivity frequency of 3·7 (95 per cent c.i. 2·8 to 4·8) per cent (*Table 2*, *Fig. 3*). The overall frequencies of nodal metastasis between the two groups (preoperative *versus* definitive diagnosis) were significantly different with an odds ratio of 2·11 (95 per cent c.i. 1·15 to 2·93).

The results of a literature search of studies that attempted to characterize a subset of patients with a biopsy diagnosis of DCIS who were at high risk of an invasive component are summarized in *Table 3*. In most such studies a palpable mass, a mammographic mass, a high-grade lesion and a large size were associated with a significant risk of invasive disease in the final resection specimen, although some inconsistencies occurred between studies.

Table 1 Frequency of sentinel nodal metastatic involvement in patients undergoing surgery with a preoperative biopsy diagnosis of ductal carcinoma *in situ*

Reference	Year	No. of patients in whom SLN biopsy was performed	No. of patients with positive SLN
Klauber-DeMore *et al.*[29]	2000	76	9 (12)
Pendas *et al.*[19]	2000	87	5 (6)
Cox *et al.*[18] updated by Wilkie *et al.*[28]	2005	559	27 (4·8)
Mittendorf *et al.*[31]	2005	41	2 (5)
Camp *et al.*[32]	2005	43	5 (12)
Yen *et al.*[33]	2005	141	12 (8·5)
Takacs *et al.*[34]	2006	44	0 (0)
Fraile *et al.*[35]	2006	142	10 (7·0)
Moran *et al.*[36]	2007	35	3 (9)
Meijnen *et al.*[37]	2007	30	5 (17)
Moore *et al.*[38]	2007	470	43 (9·1)

Values in parentheses are percentages. SLN, sentinel lymph node.

Discussion

The need for SLN biopsy in patients with a preoperative biopsy diagnosis of DCIS is controversial. In this meta-analysis of published data, the frequency of metastatic axillary lymph node involvement in patients with a preoperative diagnosis of DCIS appeared relatively high, with an overall SLN positivity of 7·4 per cent compared with 3·7 per cent in patients with a definitive (postoperative) diagnosis of DCIS. It should be noted that the main comparison cannot be randomized and so the difference may be the result of some variation in the way in which patients with a preoperative diagnosis *versus* those with a postoperative diagnosis were selected. Small patient numbers, evolving techniques of SLN biopsy and variations in methods of pathological examination, including differences in extent of tissue sampling and methods of metastasis detection, may all contribute to the variability in the reported frequencies of node positivity.

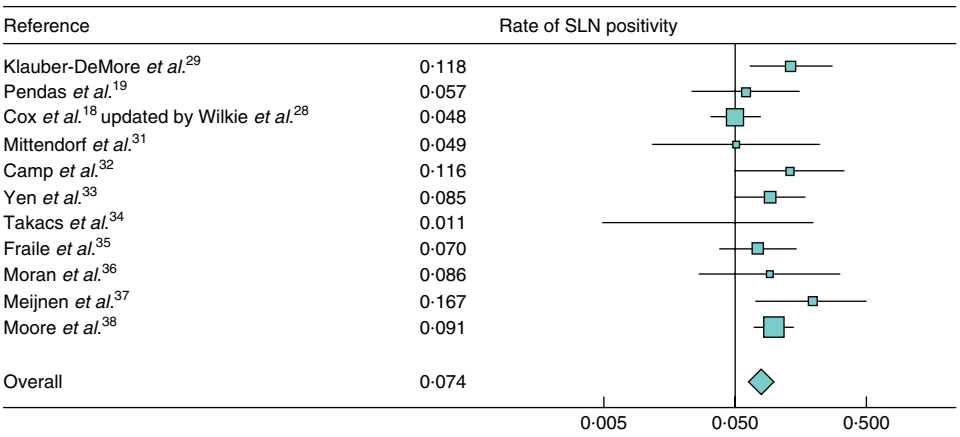

Fig. 2 Forest plot of the incidence of positive sentinel lymph node (SLN) biopsy in patients with a preoperative diagnosis of ductal carcinoma *in situ*. The sizes of the boxes are proportional to the number of patients with a positive SLN in each study. Horizontal bars represent 95 per cent confidence intervals (c.i.). The large c.i. reflect the small sample sizes in the study. The rate shown for Takacs and colleagues[34] was generated by the use of continuity correction (see text)

Table 2 Frequency of sentinel nodal involvement in patients with a postoperative diagnosis of ductal carcinoma *in situ*

Reference	Year	No. of patients in whom SLN biopsy was performed	No. of patients with positive SLN
Cserni[39]	2002	10	1 (10)
Kelly *et al.*[20]	2003	131	3 (2·3)
Intra *et al.*[21]	2003	223	7 (3·1)
Farkas *et al.*[22]	2004	44	0 (0)
Veronesi *et al.*[40]	2005	508	9 (1·8)
Zavagno *et al.*[23]	2005	102	2 (2·0)
Katz *et al.*[30]	2006	110	8 (7·2)
Mabry *et al.*[15]	2006	171	10 (5·8)
Leidenius *et al.*[41]	2006	74	5 (7)
Sakr *et al.*[42]	2006	39	4 (10)
Di Saverio *et al.*[43]	2007	32	4 (13)

Values in parentheses are percentages. SLN, sentinel lymph node.

For example, some reports doubled their node positivity frequencies by using immunohistochemistry to detect SLN involvement[14,18,30]. The differences in the reported frequencies of nodal metastases may also reflect the patient populations studied. Although most SLN biopsies in DCIS were performed in patients who were considered at high risk of harbouring invasive disease or having a mastectomy, some reports evaluated the SLN positivity frequency prospectively in patients with a preoperative biopsy diagnosis of DCIS (*Table 1*), whereas others examined this in patients who were diagnosed retrospectively with DCIS alone in the final surgical resection specimen (*Table 2*). The significant between-study heterogeneity in the 11 studies of SLN positivity of patients with a definitive (postoperative) diagnosis of DCIS could be due partly to the retrospective nature of these studies.

Some 10–30 per cent of patients with a preoperative core biopsy diagnosis of DCIS will harbour an invasive component that is not detected before surgery. This is due to inherent limitations of biopsy sampling techniques that may miss a small cancer in a large area of DCIS (*Table 3*). These patients will be upstaged to invasive cancer at final pathology. The standard of care for patients with invasive breast cancer is evaluation of the axillary lymph nodes. SLN biopsy may be offered to patients with a preoperative core biopsy diagnosis of pure DCIS, permitting those found subsequently to have invasive disease but with negative SLNs to avoid further surgery[18]. Alternatively, SLN biopsy at the time of initial operation may also preclude such biopsy at a later stage should these patients develop recurrent invasive cancer in the future[51].

It would be useful to characterize a subset of patients with a biopsy diagnosis of DCIS who are at high risk of an invasive component, in an attempt to recommend who should undergo axillary staging and be a candidate for SLN biopsy. In most studies (*Table 3*), a palpable mass, a mammographic mass, a high-grade lesion and a large size were associated with a significant risk of invasive disease in the final resection specimen. However, there are inconsistencies and so a more robust prediction model is desirable. Advocates of SLN biopsy in DCIS at the time of excision suggest that SLN biopsy may not be reliable after tumour excision and that patients should undergo an axillary lymph node dissection if a SLN biopsy was not performed at the time of the first operation[52]. However, others argue that SLN biopsy can be performed

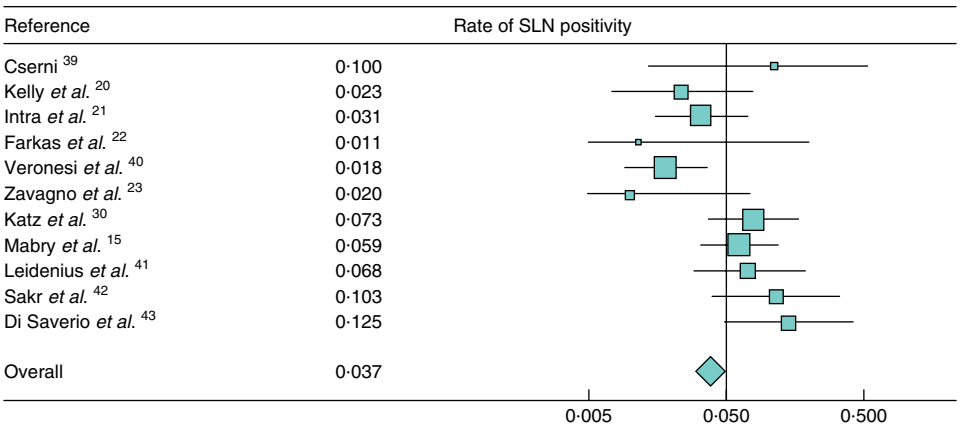

Fig. 3 Forest plot of the incidence of positive sentinel lymph node (SLN) biopsy in patients with a postoperative diagnosis of ductal carcinoma *in situ*. The sizes of the boxes are proportional to the number of patients with a positive SLN in each study. Horizontal bars represent 95 per cent confidence intervals (c.i.). The large c.i. reflect the small sample sizes in the study. The rate shown for Farkas and colleagues[22] was generated by the use of continuity correction (see text)

Table 3 Predictors of invasive disease in patients with a preoperative biopsy diagnosis of ductal carcinoma *in situ*

Reference	Total no. of patients with initial diagnosis of DCIS	No. upstaged to invasive cancer following surgical excision	Significant predictors of invasive disease	Non-significant predictors of invasive disease
36	62	20 (32)	High grade DCIS > 2·5 cm or if mastectomy was required	
44	254	21 (8·3)	Fewer than 12 core samples (size 11–14 G); comedo necrosis	
37	171	45 (26·3)	Palpable lesion; mammographic mass; intermediate grade; poorly differentiated tumour grade	
45	587	220 (37·5)	Clinically palpable mass; mammographic mass; size of clinically palpable mass and mammographic mass significant predictors on univariable analysis but not on multivariable analysis	High grade, younger age, microinvasion and comedo necrosis were not predictors of invasive cancer
46	200	41 (20·5)	Mass lesion on imaging; lesion > 1·5 cm; high nuclear grade; presence of lobular cancerization	Architectural pattern; presence of necrosis; periductal fibrosis or lymphocytic infiltrate; number of cores; extent of DCIS in cores
28	675	66 (9·8)	High-grade DCIS; mammographic mass; microinvasion	
31	30	6 (20)	Diagnosis by core-needle biopsy	Palpable lesion; grade; presence or absence of necrosis
33	398	80 (20·1)	Age ≤ 55 years; mammographic size ≥ 4 cm; grade 3 DCIS; diagnosis by core-needle biopsy	Palpable mass; pathological size; presence of comedo necrosis
26	255	41 (16·1)	Grade 3 DCIS; periductal inflammation in core biopsies; large area of calcification	Periductal stromal fibrosis
47	91	17 (19)	Comedo DCIS with cribriform/papillary pattern; DCIS > 4 mm with lobular extension	Nuclear grade; comedo necrosis; histological pattern
48	1326	183 (13·8)	Diagnosis by core-needle biopsy; mammographic mass; ≥ 10 cores per lesion	
18	240	30 (12·5)	None	Nuclear grade; comedo necrosis; histological pattern; core biopsy *versus* excisional biopsy
49	140	36 (25·7)	Mass on breast imaging	
50	140	61 (43·6)	None	Neither mammographic features nor grade were predictive
24	59	17 (29)	Inflammatory infiltrate	Nuclear grade; comedo necrosis; desmoplasia; histological pattern; no. of core biopsies, 11-G *versus* 14-G cores, size of lesion, level of suspicion, distribution and morphology of calcifications showed no difference between vacuum-assisted core and surgical biopsy

Values in parentheses are percentages. DCIS, ductal carcinoma *in situ*.

as a second procedure after lumpectomy[53,54], but not after mastectomy or a wide quadrantectomy of the upper outer quadrant, which will disrupt lymphatic pathways toward the axilla[15,23]. Patients with a preoperative diagnosis of DCIS who need a mastectomy or a wide excision close to the axilla[15,23] should, therefore, undergo a concomitant SLN biopsy. SLN biopsy in high-risk patients with DCIS has also been advocated as a tool for discovering invasive cancers with metastatic potential, which might be missed on routine histological examination of the primary tumour[39,55,56].

Another aspect of the argument against performing SLN biopsy in patients with a presumed diagnosis of DCIS is the problem of a positive SLN in this setting. The management of such patients is controversial as metastatic involvement of the SLN is frequently in the form of micrometastases (defined as small metastases no larger than 2 mm but larger than 0·2 mm) detected using immunohistochemistry

alone[21,29,30,57]. The prognostic significance and clinical consequences of micrometastases in the SLN even in invasive breast cancer remain matters of debate. The situation may represent a false-positive finding relating to microembolism of breast epithelial/tumour tissue that has been dislodged into the lymphatics by a sampling procedure or tumour massage (benign mechanical transport)[58,59]. The clinical impact of micrometastasis in the SLN for invasive breast cancer is currently under investigation in the American ACOSOG-Z0010 trial (American College of Surgeons Oncology Group) and the European IBCSG 23-01 trial (International Breast Cancer Study Group)[60]. Owing to insufficient data, and until the results of the trials become available, the guideline of the American Society of Clinical Oncology recommends routine axillary lymph node dissection for patients with micrometastases found on SLN biopsy, regardless of the method of their detection[61].

The management of node-positive patients with apparently pure DCIS in terms of further axillary treatment and/or adjuvant systemic therapy remains contentious. Although systemic treatment, including chemotherapy, has been used[21], the survival rate for pure DCIS already approaches 100 per cent and so no adjuvant systemic therapy is required[14]. In patients with a preoperative biopsy diagnosis of DCIS at high risk of harbouring invasive cancer (*Table 3*), SLN biopsy should be considered in an attempt to avoid a second operation. Patients with DCIS having a mastectomy or a large excision close to the axilla, or breast reconstruction involving the axilla, should also be considered for SLN biopsy because, should they be found to have invasive disease, sentinel node biopsy is not usually possible after such procedures.

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