Prognostic significance of occult lymph node metastases in breast cancer: a meta-analysis

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Abstract

Background: Occult metastases in axillary lymph nodes have been reported to be associated with poor prognosis in patients with breast cancer. However, studies on the prognostic value of occult metastases remain controversial. This meta-analysis aimed to evaluate the prognostic significance of occult lymph node metastases in breast cancer.

Methods: Studies published until May, 2020, which retrospectively examined negative lymph nodes by step sectioning and/or immunohistochemistry, were retrieved from MEDLINE, EMBASE, CNKI, and Cochrane Library. The pooled Relative risk (RR) with 95% confidence interval (95% CI) for overall survival (OS) and disease-free survival (DFS) were calculated to appraise the associations between occult metastases and prognosis.

Results: The results showed patients with occult metastases in axillary lymph nodes had poorer five-year DFS (RR = 0.930; 95% CI = 0.907–0.954) and OS (RR = 0.972; 95% CI = 0.954–0.990). Furthermore, the DFS (RR = 0.887; 95% CI = 0.810–0.972) and OS (RR = 0.896; 95% CI = 0.856–0.939) of patients with occult metastases were much lower after a ten-year follow-up.

Conclusions: Occult metastases in the axillary lymph nodes of patients with breast cancer are associated with poorer disease-free and overall survival. Occult metastases might serve as a predictive factor of survival outcomes in patients with breast cancer.

Background

Axillary lymph node (ALN) status is an important prognostic indicator of survival in breast cancer[1]. In 1948, Saphir et al. showed that a limited number of sections from the axillary lymph nodes of patients with breast cancer are insufficient to detect metastases[2]. Since then, occult metastases have been defined as which were not initially assessed, but detected by further examinations[3]. Over the following decades, multiple new techniques have been introduced to improve lymph node biopsy. Using step-sectioning and immunohistochemical (IHC) staining, occult metastases have been frequently detected in 12–23% of women with breast cancer, who initially exhibit negative axillary lymph nodes on H&E staining during routine pathologic examination[4–10]. In addition, some studies also used reverse transcriptase-polymerase chain reaction (RT-PCR) to detect specific mRNA[6, 7, 11].

The prognostic significance of occult metastases remains controversial. Although several previous studies indicated occult metastases impacts OS or DFS[9, 12–15], others argued that occult metastases have no significant prognostic value [6, 10, 16, 17]. Furthermore, the routine use of IHC to stage lymph nodes is also questioned in recent large studies. The National Surgical Adjuvant Breast and Bowel Project randomized controlled trial B-32 (NSABP B-32) indicated that occult metastases were an independent prognostic variable in survival, however, the difference in outcome at 5 years was small (1.2 percentage points)[14]. The American College of Surgeons Oncology Group (ACOSOG) Z0010 study also demonstrated that IHC evidence of occult metastases was not significantly associated with overall survival[18]. As a result of these studies, the current National Comprehensive Cancer Network (NCCN) guideline for breast cancer does not recommend routine IHC to define node involvement[19]. Although several previous system review have been published on the association between occult metastases and survival[3, 16], an update including recent evidences is still necessary. This study aimed to systematically evaluated the association between occult lymph node metastases and survival among patients with breast cancer.

Methods

Search strategy

The literature review was performed in PUBMED, EMBASE, China National Knowledge Infrastructure (CNKI), and Cochrane Library until December 1, 2018. The following search terms were used: (breast cancer OR breast carcinoma OR breast neoplasms), (lymph node OR lymph-node), (occult metastases OR micrometastases OR isolated tumor cells), and (prognosis OR prognostic OR survival OR survival rate OR survival analysis OR mortality OR recurrence). Relevant reviews, meta-analyses, and references cited in these papers were also checked for potential studies. Abstracts or unpublished reports were not considered. If more than one article was published by the same author using the same case series, the study with the highest number of subjects was selected. All the searches were conducted by two reviewers independently, and any disagreement was resolved through discussion.

Inclusion And Exclusion Criteria

The following inclusion criteria were applied: evaluation of the association between occult metastases and survival outcome of breast cancer patients, case-control or cohort design, description of the survival outcomes of the studies in terms of disease-free or overall
survival, and full texts based on original data. The exclusion criteria employed were: no control group (lymph node-negative group), lack of Kaplan-Meier methods or life-table analyses, and short follow-up period (< 5 years).

Data Extraction And Study Quality Assessment

All data were extracted independently by two reviewers, according to pre-specified selection criteria. Disagreement was resolved by consensus and discussion with the third investigator. The following data were extracted: pathological assessment of the removed lymph nodes, number of control group, number of patients with lymph node occult metastases, tumor stage, follow-up period, performance of axillary lymph node dissection, disease-free/overall survival rates, administration of adjuvant systemic therapy, and results of multivariable analyses (Table 1). If the survival data were not provided in a table or text in the chosen articles, they would be extracted from the survival curves by Engauge Digitizer version 10.8 (GitHub, Open Source software). To prevent overlap of the data from studies that described subpopulations besides a total population, only subpopulations were taken into account for the calculation of relative risks. The Newcastle-Ottawa scale (NOS) was applied to assess the quality of the study[20].
<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Year</th>
<th>PA</th>
<th>No. of patient</th>
<th>Stage</th>
<th>% AST</th>
<th>FU, y</th>
<th>Survival, % (OM vs pN0)</th>
<th>NOS</th>
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<tr>
<td>Fisher ER[23]</td>
<td>1978</td>
<td>SS (20µm), H&amp;E</td>
<td>19</td>
<td>59</td>
<td>I</td>
<td>0</td>
<td>0 5.1 a*</td>
<td>71 vs 68</td>
</tr>
<tr>
<td>Rosen PP[24]</td>
<td>1982</td>
<td>SS (48µm), H&amp;E</td>
<td>9</td>
<td>19</td>
<td>I</td>
<td>0</td>
<td>0 NR</td>
<td>89 vs 69</td>
</tr>
<tr>
<td>Wilkinson E[25]</td>
<td>1982</td>
<td>SS (24–48 µm), H&amp;E</td>
<td>89</td>
<td>436</td>
<td>NR</td>
<td>0</td>
<td>0 5 min</td>
<td>- 82 vs 80</td>
</tr>
<tr>
<td>IBCSG[15] (no peri-op CT)</td>
<td>1990</td>
<td>SS (48µm), H&amp;E (6 levels)</td>
<td>55</td>
<td>555</td>
<td>II</td>
<td>0</td>
<td>0 5 med</td>
<td>61 vs 76</td>
</tr>
<tr>
<td>IBCSG[15] (peri-op CT)</td>
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<td>SS (48µm), H&amp;E (6 levels)</td>
<td>30</td>
<td>283</td>
<td>II</td>
<td>100 100</td>
<td>5 med</td>
<td>54 vs 68</td>
</tr>
<tr>
<td>Gelea MH[4]</td>
<td>1991</td>
<td>H&amp;E + IHC (2 levels)</td>
<td>9</td>
<td>89</td>
<td>IIA</td>
<td>0</td>
<td>0 NR</td>
<td>- 100 vs 74</td>
</tr>
<tr>
<td>de Mascarel[26]</td>
<td>1992</td>
<td>SS (1500µm), H&amp;E (1 level)</td>
<td>120</td>
<td>785</td>
<td>III</td>
<td>0</td>
<td>0 6.9 med</td>
<td>80 vs 88</td>
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<tr>
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<td>1993</td>
<td>IHC (2 levels)</td>
<td>20</td>
<td>77</td>
<td>NR</td>
<td>0</td>
<td>0 5.7 a*</td>
<td>69 vs 71</td>
</tr>
<tr>
<td>Hainworth PJ[28]</td>
<td>1993</td>
<td>IHC (1 level)</td>
<td>41</td>
<td>302</td>
<td>III</td>
<td>0</td>
<td>0 6.6 med</td>
<td>68 vs 84</td>
</tr>
<tr>
<td>Nasser IA[29] (&lt; 0.2 mm)</td>
<td>1993</td>
<td>SS (150µm), H&amp;E (5 levels) + IHC (1 level)</td>
<td>31</td>
<td>109</td>
<td>NR</td>
<td>0</td>
<td>0 11 a*</td>
<td>93 vs 81</td>
</tr>
<tr>
<td>Nasser IA[29] (&gt; 0.2 mm)</td>
<td>1993</td>
<td>SS (150µm) H&amp;E (5 levels) + IHC (1 level)</td>
<td>19</td>
<td>109</td>
<td>NR</td>
<td>0</td>
<td>0 11 a*</td>
<td>62 vs 81</td>
</tr>
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<td>1996</td>
<td>IHC (3 levels)</td>
<td>3</td>
<td>182</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR 100 vs 91</td>
</tr>
<tr>
<td>Clare SE[31]</td>
<td>1997</td>
<td>SS (150µm) H&amp;E + IHC (5 levels)</td>
<td>11</td>
<td>75</td>
<td>NR</td>
<td>0</td>
<td>0 6.7 med</td>
<td>71 vs 84</td>
</tr>
<tr>
<td>Gerber B[32]</td>
<td>1997</td>
<td>H&amp;E + IHC (2–6 levels)</td>
<td>18</td>
<td>141</td>
<td>IIA</td>
<td>68 100</td>
<td>4.3 a</td>
<td>70 vs 86</td>
</tr>
</tbody>
</table>

PA = pathological assessment of lymph nodes after original pathological assessment; AST = adjuvant systemic therapy; FU = follow up; DFS = disease-free survival; OS = overall survival; OM = occult breast cancer metastasis; MVA = multivariable analysis; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; ITC = isolated tumor cell ≤ 0.2 mm in diameter; mi = micrometastases from > 0.2 mm to ≤ 2 mm; H&E = hematoxylin and eosin staining; SS = step sectioning; IHC = immunohistochemical staining; NR = not reported; a* = average; min = minimum; med = median; NOS = Newcastle-Ottawa scale score.
<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Year</th>
<th>PA</th>
<th>No. of patient</th>
<th>Stage</th>
<th>% AST</th>
<th>FU, y</th>
<th>Survival, % (OM vs pN0)</th>
<th>NOS</th>
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<tr>
<td>Cote RJ[33]</td>
<td>1999</td>
<td>IHC (1 level)</td>
<td>148</td>
<td>588</td>
<td>I-II</td>
<td>12 med</td>
<td>69 vs 74</td>
<td>-</td>
</tr>
<tr>
<td>Braun S[11]</td>
<td>2001</td>
<td>IHC (3 levels)</td>
<td>13</td>
<td>137</td>
<td>I-II</td>
<td>0 0</td>
<td>4 med</td>
<td>91 vs 83</td>
</tr>
<tr>
<td>Cummings MC[34]</td>
<td>2002</td>
<td>SS (100µm) H&amp;E + IHC (4 levels)</td>
<td>53</td>
<td>150</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>10.3 med</td>
</tr>
<tr>
<td>de Mascarel [35]</td>
<td>2002</td>
<td>SS (1500µm) H&amp;E + IHC (1 level)</td>
<td>13</td>
<td>116</td>
<td>NR</td>
<td>0 0</td>
<td>24 med</td>
<td>84 vs 94</td>
</tr>
<tr>
<td>de Mascarel <a href="ILC">35</a></td>
<td>2002</td>
<td>SS (1500µm) H&amp;E + IHC (1 level)</td>
<td>37</td>
<td>52</td>
<td>NR</td>
<td>0 0</td>
<td>18 med</td>
<td>91 vs 94</td>
</tr>
<tr>
<td>Fisher ER[36]</td>
<td>2002</td>
<td>IHC (of original H&amp;E)</td>
<td>63</td>
<td>213</td>
<td>I-II</td>
<td>100 100</td>
<td>9a*</td>
<td>-</td>
</tr>
<tr>
<td>Millis RR[6] (ITC)</td>
<td>2002</td>
<td>HE&amp;IHC (1 level)</td>
<td>23</td>
<td>417</td>
<td>NR</td>
<td>0 0</td>
<td>13.2 (OM) 18.9 (pN0) med</td>
<td>-</td>
</tr>
<tr>
<td>Millis RR[6] (mi)</td>
<td>2002</td>
<td>HE&amp;IHC (1 level)</td>
<td>57</td>
<td>417</td>
<td>NR</td>
<td>0 0</td>
<td>13.2 (OM) 18.9 (pN0) med</td>
<td>-</td>
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<tr>
<td>Umekita Y[13]</td>
<td>2002</td>
<td>IHC</td>
<td>21</td>
<td>127</td>
<td>NR</td>
<td>100 100</td>
<td>8.2 med</td>
<td>75 vs 95</td>
</tr>
<tr>
<td>Gebauer G[37]</td>
<td>2003</td>
<td>examination SS (H&amp;E 6 levels), followed by H&amp;E + IHC (2 levels)</td>
<td>14</td>
<td>198</td>
<td>NR</td>
<td>0 0</td>
<td>NR</td>
<td>86 vs 88</td>
</tr>
<tr>
<td>Reed W[7] (ITC)</td>
<td>2004</td>
<td>IHC (1 level)</td>
<td>21</td>
<td>340</td>
<td>I-HIA</td>
<td>0 0</td>
<td>25.6 med</td>
<td>-</td>
</tr>
<tr>
<td>Reed W[7] (mi)</td>
<td>2004</td>
<td>IHC (1 level)</td>
<td>16</td>
<td>340</td>
<td>I-HIA</td>
<td>0 0</td>
<td>25.6 med</td>
<td>-</td>
</tr>
<tr>
<td>Kahn HJ[38]</td>
<td>2006</td>
<td>IHC (1 level)</td>
<td>29</td>
<td>175</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>8 med</td>
</tr>
<tr>
<td>Marinho VF[39]</td>
<td>2006</td>
<td>IHC</td>
<td>26</td>
<td>162</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6.8 med</td>
</tr>
</tbody>
</table>

PA = pathological assessment of lymph nodes after original pathological assessment; AST = adjuvant systemic therapy; FU = follow up; DFS = disease-free survival; OS = overall survival; OM = occult breast cancer metastasis; MVA = multivariable analysis; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; ITC = isolated tumor cell ≤ 0.2 mm in diameter; mi = micrometastases from > 0.2 mm to ≤ 2 mm; H&E = hematoxylin and eosin staining; SS = step sectioning; IHC = immunohistochemical staining; NR = not reported; a* = average; min = minimum; med = median; NOS = Newcastle-Ottawa scale score.
### Statistical analysis

The five- and ten-year relative risk (RR) of disease-free and overall survival was compared between the occult metastases group and control (lymph node negative) group. Statistical heterogeneity was measured using $I^2$ ($I^2 > 50\%$ was considered statistically significant heterogeneity). If significant heterogeneity was detected, the random-effects model was used and sensitivity analysis performed by removing one study at a time to calculate overall homogeneity and effect size. Otherwise, a fixed-effects model was employed\cite{21}.

Egger's regression method was used statistically to assess publication bias ($p < 0.05$ was considered statistically significant)\cite{22}.

Statistical analysis was performed using STATA version 12.0 (StataCorp LLC, US), 95% confidence intervals (CIs) were reported, and $p < 0.05$ was considered statistically significant. All statistical tests were two-sided.

### Results

#### Studies included in the meta-analysis
A total of 487 papers were identified as relevant to the search words. After screening the title and reading the abstract, 134 articles were selected to for full text review, 26 studies were excluded as review or meta-analysis, and 77 articles were removed for not involving survival data or prognostic results. In further analysis of the remaining 31 potential articles, two articles were excluded: one reported duplicate data and the other one had insufficient data. Finally, 29 publications with 105060 patients were included[4, 6–15, 23–40]. The flowchart of selection of studies and reasons for exclusion is presented in Fig. 1.

The characteristics and quality assessment results of the articles selected are summarized in Table 1. Of these, five articles only took step sectioning[15, 23–26], nine used step sectioning combined with immunohistochemical staining[8, 9, 12, 14, 29, 31, 34, 35, 37], four applied hematoxylin and eosin (H&E) staining with immunohistochemical staining[4, 6, 10, 32], while the rest only utilized immunohistochemical staining[7, 11, 13, 27, 28, 30, 33, 36, 38–40]. The breast cancer stage was described detailly in only 13 articles[4, 7, 10–12, 15, 20, 23, 24, 26, 28, 32, 33, 36], and follow-up duration ranged from 3.1 to 25.6 years. The use of adjuvant systemic therapy was not reported in 8 articles[14, 30, 31, 33, 34, 38–40], while it was applied to all or some patients in 7 articles[9, 10, 12, 13, 15, 32, 36], and none in the rest. Among the included articles, seven divided the patients with occult metastases into different subgroups[7–9, 12, 15, 29, 35]. As all subgroups analysis were regarded as separated studies, 36 studies were chosen for evaluation in this meta-analysis.

Association Between Occult Metastases And Survival Of Patients

After a five-year follow-up, the results showed that occult metastases group was associated with poorer DFS (RR = 1.497; 95% CI = 1.341–1.671; \( I^2 = 28.6\% \) ) (Fig. 2) and OS (RR = 1.440; 95% CI = 1.186–1.749; \( I^2 = 71.7\% \) ) (Fig. 3). After a ten-year follow-up, the results also revealed poorer DFS (RR = 1.688; 95% CI = 1.256–2.268; \( I^2 = 66.2\% \) ) (Fig. 4) and OS (RR = 1.477; 95% CI = 1.279–1.705; \( I^2 = 58.3\% \) ) (Fig. 5) in patients with occult metastases. As obvious heterogeneity was observed in the study of 5-yr OS and 10-yr FDS, a random-effects model was utilized in these analysis. The results of the sensitivity analysis were consistent after excluding several studies[14, 33], with the confidence interval of RR not significantly decreasing (Fig. 6).

Evaluation Of Publication Bias

As including almost all studies, the studies of 5-yr DFS were conducted by using funnel plots and Egger’s test to assess publication bias. The funnel plot was approximately symmetrical (Fig. 7) and the result of Egger’s test (P = 0.567) revealed no obvious publication bias among the studies.

Discussion

Our meta-analysis analyzed 36 studies to explore the association between occult metastases in axillary lymph nodes and long-term prognosis for patients with breast cancer. In pooled analyses, occult metastases were associated with worse disease-free and overall survival than a lymph node negative state after both five and ten years’ follow-up. These results demonstrated that occult metastases could be an independent prognostic factor in breast cancer patients with negative nodes on initial biopsy. Although the result of the sensitivity analysis were consistent, the occult metastasis still showed a much worse prognosis after excluding the study conducted by Weaver et al[14]. This heterogeneity might be due to the second largest sample size and the relatively smaller difference in 5-year survival. Nevertheless, although these studies differed in terms of patient population, pathological assessment, follow-up duration, and methodology, their results were generally homogenous. Although this is not the first meta-analysis to evaluate the relationship between occult metastases and survival in patients with breast cancer, this study has several strengths over the previous meta-analysis[3]. The previous meta-analysis pointed out that presence of occult metastases was associated with poorer disease-free survival and overall survival. Our current meta-analysis added recent large studies and obtain consistent results\textsuperscript{14,20}.

The results were predominantly consistent with two previous large studies, which have demonstrated that patients with occult micrometastases in axillary lymph nodes had a poorer survival\textsuperscript{14,40}. Weaver et al[14] found that occult metastases were an independent prognostic factor in patients with sentinel lymph nodes that were negative on initial examination. However, they indicated the additional evaluation, including immunohistochemical analysis, had no clinical benefit because the difference between survival were statistically significant but relatively small. A larger study including 93,070 patients also demonstrated a difference in OS between patients with occult metastases and those with IHC-negative lymph nodes\textsuperscript{40}. However, in further multivariate analysis in subgroups, micrometastases (0.2–2 mm diameter), rather than isolated tumor cells (< 0.2 mm diameter or < 200 cells), remained an independent predictor for survival.

Our results differ from those of ACOSOG Z0010 study, which demonstrated no obvious difference in 5-year OS between occult metastases and no metastase\textsuperscript{18}. The difference might be due to that ACOSOG Z0010 was limited to early-stage T1 and T2 tumors.
Several studies included in our analysis also reported that occult metastases could not predict a poorer survival in patients with breast cancer [6, 11, 23, 24, 35, 38]. This lack of significant difference might be due to the small sample size and the earlier pathological examination techniques.

Our analysis of the selected studies revealed that occult metastases could be detected in 9–42% of patients with breast cancer [4, 6–15, 23–40], mostly with micrometastasis and isolated tumor cells, whereas macrometastases were still inevitable. Weaver et al. [14] reported that the hazard ratio for death was 1.38 (95% CI = 1.02–1.87) in patients with isolated tumor cells and 1.91 (95% CI = 1.41–2.59) in those with micrometastases or macrometastases, when compared with patients in whom occult metastases were not detected. Hence, this study suggested that improvement of intraoperative assessment is necessary for the clinical pathologist to increase the metastasis detection rate, especially macrometastases of > 2 mm. In addition to intraoperative frozen section analysis, molecular techniques, such as transcriptase-polymerase chain reaction and one-step nucleic acid amplification have been utilized, which could contribute to better detection rate of lymph nodes metastases, tumor staging, and subsequent therapeutic strategy [41].

The limitations of this study are as follows: (1) this meta-analysis based on data from survival curve curves instead of pooled individual data; (2) pathological type, surgical Options, adjuvant treatment regimen, and systemic Therapy may be associated with DFS and OS, while these detail data were not available in mostly included studies or unable to conduct stratified analysis; (3) most included studies had a retrospective design, so recall and selection biases might affect the result; (4) publication bias is an inevitable problem since this study is based on published articles, and ongoing or unpublished studies were not included in this meta-analysis.

**Conclusions**

In summary, we found that occult metastases in the axillary lymph nodes of patients with breast cancer are an independent predictor of disease-free and overall survival. Moreover, it may indicate a relatively poor prognosis. However, because of non-standardized pathological examination and treatment, the prognostic value of occult metastases is still limited and further extensive studies are needed.

**List Of Abbreviations**

RR: relative risk

95% CI: 95% confidence interval

OS: overall survival

DFS: disease-free survival

ALN: axillary lymph node

IHC: immunohistochemical

RT-PCR: reverse transcriptase-polymerase chain reaction

ACOSOG: American College of Surgeons Oncology Group

NCCN: National Comprehensive Cancer Network

CNKI: China National Knowledge Infrastructure

NOS: Newcastle-Ottawa scale

H&E: hematoxylin and eosin

**Declarations**

Ethics approval and consent to participate

Not applicable.
Consent for publication
Not applicable.

Availability of data and materials
All data generated or analysed during this study are included in this published article.

Competing interests
The authors declare that they have no competing interests.

Funding
Not applicable.

Authors' contributions
Guixin Wang, Shuhao Zhang and Haidong Zhao designed this study. Meiling Wang, Lin Liu, Yaqian Liu, Lianjun Tang and He Bai collected and analyzed the data. Guixin Wang and Shuhao Zhang drafted the manuscript. Haidong Zhao interpreted the data and revised the manuscript. All authors have read and approved the final manuscript.

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References


Figures

Flowchart of selection of studies and specific reasons for exclusion from the meta-analysis.
Figure 2

Association between 5-y DFS and the present of occult ALN metastasis.
Figure 3

Association between 5-y OS and the present of occult ALN metastasis.
Figure 4

Association between 10-y DFS and the present of occult ALN metastasis.
Figure 5

Association between 10-y OS and the present of occult ALN metastasis.
Figure 6

Results of the sensitivity analysis. Results when each study is excluded are shown by the point estimate of the HR and 95% CI.
Figure 7

Funnel plot analysis on the detection of publication bias in the meta-analysis of Prognostic Significance of Occult Lymph Node Metastases in breast cancer.