Low number of examined lymph nodes in node-negative breast cancer patients is an adverse prognostic factor

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Received 3 May 2006; revised 14 June 2006; accepted 16 June 2006

Background: The aim of the study was to determine whether the number of lymph nodes removed at axillary dissection is associated with recurrence and survival in node-negative breast cancer (NNBC) patients.

Patients and methods: We retrospectively reviewed the medical records of 1606 women with pathologically node-negative T1–T3 invasive breast cancer. Median follow-up was 61 months (range 2–251). Potential prognostic factors assessed included: number of axillary lymph nodes examined, age, menopausal status, tumor size, histological type, tumor grade, estrogen receptor(ER), progesterone receptor (PR) and HER2.

Results: At 5 years, relapse-free survival (RFS) rate was 85% and breast cancer-specific survival (BCSS) rate was 94%. In univariate analysis, factors significantly associated with lower RFS and BCSS were: fewer than six lymph nodes examined (RFS, \(P = 0.01\); BCSS, \(P = 0.007\)), tumor size >2 cm, grade III, negative ER or PR. Statistically significant factors for lower RFS and BCSS in multivariate analysis were: fewer than six lymph nodes examined [RFS, hazard ratio (HR) 1.36, \(P = 0.029\); BCSS, HR 1.87, \(P = 0.005\)], tumor size >2 cm, tumor grade III and negative PR.

Conclusions: Examination of fewer than six lymph nodes is an adverse prognostic factor in NNBC because it could lead to understaging. Six or more nodes need to be examined at axillary dissection to be confident of a node-negative status. This may be useful, in conjunction with other prognostic factors, in the assessment of NNBC patients for adjuvant systemic therapy.

Key words: breast, cancer, lymph, nodes, number, prognosis

Introduction

In recent years, owing to breast cancer screening programs, node-negative breast cancer (NNBC) has become more common [1]. Approximately 30% of these patients will have disease relapse [2] so systemic adjuvant systemic treatments are often used to reduce the risk of recurrence [3]. However, only a minority of these patients will benefit from adjuvant systemic therapy. Locoregional management alone will cure a large proportion of NNBC patients [4]. Therefore, it is reasonable to apply prognostic factors to this patient population to identify those at higher risk of relapse who will potentially benefit most from adjuvant systemic treatment.

Axillary lymph node dissection (ALND) is still considered part of the standard management of operable breast cancer and remains routine practice in many parts of the world [5]. It has been debated whether it is necessary to perform a complete lymphadenectomy [6, 7] or if sampling of the axilla is enough [8, 9]. Several studies have reported an association between the number of nodes removed at ALND and survival [10–16] and thus provide recommendations on the minimum number of evaluable nodes required to be confident about node-negative status [17]. Conversely, only one study has described worse outcomes with removal of a greater number of lymph nodes [18]. Currently, the Union Internationale Contre Cancer (UICC/AJCC) Tumor/Node/Metastasis (TNM) classification requires the removal and analysis of at least the proximal axillary nodes (level I), which should yield a minimum of six nodes, to assign a pathologic nodal stage [19]. However, the recent development of sentinel lymph node biopsy and the increasing use of adjuvant systemic therapies have provided a rationale for the omission of complete axillary lymphadenectomy [20, 21].

In the light of these data, further study of the prognostic significance of ALND in conjunction with other prognostic factors in the assessment of NNBC patients for adjuvant systemic therapy is needed. Therefore, the purpose of the current study was to assess the number of axillary nodes examined in NNBC patients and to analyze whether examination of fewer than six nodes was related to a higher risk of relapse and to a shorter breast cancer-specific survival.
patients and methods

Subjects were patients with NNBC diagnosed between 1 January 1982 and 31 December 2000 who were treated at Clinic Hospital, University of Valencia, Spain. Patients were ineligible if they had in situ disease, a T4d primary tumor, axillary nodal involvement, bilateral breast cancer or distant metastases. Eligible patients had to have survived at least 30 days from the time of diagnosis, to have undergone an axillary dissection with at least one lymph node recovered (not eligible if a sentinel lymph node biopsy was performed), and to have received no neoadjuvant systemic treatment. The research ethics committee of the hospital oversaw the project and a waiver of informed consent was obtained.

The study includes all eligible patients treated at the institution between 1982 and 2000, so it represents a sequential series of cases. Data were collected by retrospective review of pathology reports. In the processing of the pathologic nodal specimens, immunohistochemical analysis for occult metastases was not routinely performed. We considered, on the basis of UICC/AJCC recommendations [19], the following two groups in our analysis of the number of lymph nodes examined: patients with one to five lymph nodes removed and those with six or more lymph nodes removed. Other prognostic factors extracted from a retrospective review of patient medical records were age and menopausal status at diagnosis, tumor size (maximum histological or gross pathologic size in mm), histological type, tumor grade (according to Scarf–Bloom–Richardson [22, 23]), estrogen receptor (ER) status (negative or positive), progesterone receptor (PR) status (negative or positive), and HER2 status (negative or positive).

During the period of the study, our standard clinical practices following breast and axillary surgery for NNBC were as follows.

(i) Local radiotherapy when breast-conserving surgery was performed.
(ii) Locoregional radiotherapy when the tumor was larger than 5 cm.
(iii) The criteria adopted for prescribing adjuvant systemic therapy were as follows. Chemotherapy when two or more of the following features were present: tumor size larger than 2 cm, age younger than 35 years and tumor grade III.
(iv) After the surgery or the chemotherapy (when it was administered), hormonal therapy was given in cases where ER and/or PR status were positive or unknown. The agent of choice was tamoxifen, 20 mg/day for 5 years.

Patients were divided into the following groups depending on the type of systemic therapy received: (1) no systemic treatment; (2) only hormonal therapy; (3) chemotherapy with anthracyclines; (4) chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF); and (5) other chemotherapy schedules.

statistical analysis

Overall survival (OS) was measured from the date of diagnosis to the date of death from any cause or last follow-up. Breast cancer-specific survival (BCSS) was measured from the date of diagnosis to the date of death from breast cancer or last follow-up. Patients who died from other causes were considered censored for BCSS. Relapse-free survival (RFS) was measured from the date of diagnosis to the date of relapse (local or systemic) or last follow-up. Patients who died before experiencing a relapse were censored at their date of death for RFS.

RFS, BCSS, and OS were estimated using the Kaplan–Meier method [24]. The statistical significance of the difference between survival times was determined by the log-rank test in the univariate analysis. Multivariate tests were performed with Cox proportional hazards analysis [25]. The number of lymph nodes recovered was categorized as one to five or more than five for the tables, log-rank test and Cox analysis. We considered a result to be statistically significant when $P < 0.05$. The confidence interval (CI) used for survival was 95%.

results

We identified a total of 1668 patients with NNBC, but several were excluded for the following reasons: six patients had Paget’s histological type, nine did not have a pathology report and 47 were without follow-up data. Therefore, we included 1606 patients in the current analysis. The characteristics of the population and their systemic adjuvant treatments are shown in Table 1. The median number of lymph nodes examined was 12 (range 1–54 nodes).

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median: 57 years (21–98)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤35 years</td>
<td>76</td>
<td>4.7</td>
</tr>
<tr>
<td>&gt;35 years</td>
<td>1530</td>
<td>95.3</td>
</tr>
<tr>
<td>Hormonal menopausal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>524</td>
<td>32.6</td>
</tr>
<tr>
<td>Perimenopausal</td>
<td>45</td>
<td>2.8</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1037</td>
<td>64.6</td>
</tr>
<tr>
<td>Tumor size, median: 21 mm (1–100)</td>
<td></td>
<td></td>
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<tr>
<td>≤20 mm</td>
<td>800</td>
<td>49.8</td>
</tr>
<tr>
<td>&gt;20 mm</td>
<td>806</td>
<td>50.2</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltrating ductal carcinoma</td>
<td>1300</td>
<td>81.9</td>
</tr>
<tr>
<td>Infiltrating lobular carcinoma</td>
<td>124</td>
<td>7.8</td>
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<tr>
<td>Others: medullary, mucinous, apocrine, tubular, papillary</td>
<td>164</td>
<td>10.3</td>
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<tr>
<td>Unknown</td>
<td>18</td>
<td>1.1</td>
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<td>Estrogen receptor status</td>
<td></td>
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<tr>
<td>Positive</td>
<td>719</td>
<td>44.8</td>
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<tr>
<td>Negative</td>
<td>414</td>
<td>25.8</td>
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<tr>
<td>Unknown</td>
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<td>29.5</td>
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<td>Progesterone receptor status</td>
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<tr>
<td>Negative</td>
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<td>29.6</td>
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<td>30.1</td>
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<td>Overexpression HER2</td>
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<td>Positive</td>
<td>54</td>
<td>3.4</td>
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<td>Negative</td>
<td>668</td>
<td>41.6</td>
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<td>Unknown</td>
<td>884</td>
<td>55</td>
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<tr>
<td>Examined nodes, median: 12 (1–54)</td>
<td></td>
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<tr>
<td>≤5 nodes</td>
<td>230</td>
<td>14.3</td>
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<td>&gt;5 nodes</td>
<td>1240</td>
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<td>Systemic adjuvant treatment</td>
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<td>None</td>
<td>172</td>
<td>10.7</td>
</tr>
<tr>
<td>Only hormonal therapy</td>
<td>610</td>
<td>38</td>
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<tr>
<td>Chemotherapy with anthracyclines</td>
<td>726</td>
<td>45</td>
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<tr>
<td>CMF chemotherapy</td>
<td>51</td>
<td>3.2</td>
</tr>
<tr>
<td>Other chemotherapy schedules</td>
<td>47</td>
<td>2.9</td>
</tr>
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</table>

CMF, cyclophosphamide, methotrexate and 5-fluorouracil.
With a median follow-up of 61 months (range 2–251 months), 276 relapses (17.2%) and 126 deaths (7.8%) from breast cancer were observed. The RFS rate at 5 years was 85% (95% CI 81–87) and at 10 years was 72% (95% CI 69–75). The mean RFS duration was 187 months (95% CI 179–194). The BCSS rate at 5 years was 94% (95% CI 93–95) and at 10 years was 86% (95% CI 84–89). The mean BCSS duration was 219 months (95% CI 214–225). The OS rate at 5 years was 91% (95% CI 89–93) and at 10 years was 80% (95% CI 77–83). The mean OS duration was 205 months (95% CI 199–211).

The mean RFS, 5- and 10-year RFS rates, and the significant results of the univariate analysis for variables associated with RFS are listed in Table 2. It can be observed that RFS was shorter with examination of five or fewer lymph nodes (Figure 1, \(P = 0.014\)). The mean BCSS, 5- and 10-year BCSS rates, and the results of the univariate analysis for variables associated with BCSS are also listed in Table 2. The examination of fewer than six axillary lymph nodes was associated with a significantly shorter BCSS (Figure 2, \(P = 0.007\)).

Factors found to be significantly associated with shorter RFS in the multivariate Cox regression analysis are listed in Table 3. The examination of fewer than six lymph nodes was associated with worse RFS [hazard ratio, 1.44 (95% CI 1.03–2.00)]. Factors found to be significantly associated with lower BCSS in the multivariate Cox regression analysis are also listed in Table 3. The examination of fewer than six lymph nodes was associated with worse BCSS [hazard ratio, 1.87 (95% CI 1.20–2.91)].

**Table 2.** Mean, 5-year, 10-year and \(P\) values by variable in log-rank tests for RFS and BCSS

<table>
<thead>
<tr>
<th>Variable</th>
<th>RFS 5 years (%)</th>
<th>RFS 10 years (%)</th>
<th>RFS Mean (months)</th>
<th>(P) value</th>
<th>BCSS 5 years (%)</th>
<th>BCSS 10 years (%)</th>
<th>BCSS Mean (months)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5 removed nodes</td>
<td>82</td>
<td>63</td>
<td>161</td>
<td>0.014</td>
<td>90</td>
<td>83</td>
<td>139</td>
<td>0.007</td>
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<tr>
<td>&gt;5 removed nodes</td>
<td>86</td>
<td>74</td>
<td>171</td>
<td></td>
<td>95</td>
<td>87</td>
<td>222</td>
<td></td>
</tr>
<tr>
<td>Age &lt;36 years</td>
<td>65</td>
<td>52</td>
<td>134</td>
<td>0.000</td>
<td>88</td>
<td>79</td>
<td>209</td>
<td>0.16</td>
</tr>
<tr>
<td>Age ≥36 years</td>
<td>86</td>
<td>73</td>
<td>190</td>
<td></td>
<td>94</td>
<td>87</td>
<td>219</td>
<td></td>
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<tr>
<td>Premenopausal status</td>
<td>83</td>
<td>70</td>
<td>179</td>
<td>0.613</td>
<td>94</td>
<td>86</td>
<td>223</td>
<td>0.64</td>
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<td>Perimenopausal status</td>
<td>86</td>
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<td>151</td>
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<td>88</td>
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<td>Postmenopausal status</td>
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<td>177</td>
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<td>94</td>
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<td>207</td>
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<tr>
<td>Tumor size ≤20 mm</td>
<td>88</td>
<td>77</td>
<td>184</td>
<td></td>
<td>96</td>
<td>90</td>
<td>212</td>
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<tr>
<td>Tumor size &gt;20 mm</td>
<td>83</td>
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<td>92</td>
<td>84</td>
<td>213</td>
<td>0.002</td>
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<td>Histologic type</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Infiltrating ductal carcinoma</td>
<td>84</td>
<td>70</td>
<td>184</td>
<td>0.006</td>
<td>94</td>
<td>85</td>
<td>218</td>
<td>0.277</td>
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<tr>
<td>Infiltrating lobular carcinoma</td>
<td>88</td>
<td>80</td>
<td>164</td>
<td></td>
<td>97</td>
<td>91</td>
<td>205</td>
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<tr>
<td>Others</td>
<td>90</td>
<td>84</td>
<td>197</td>
<td></td>
<td>94</td>
<td>91</td>
<td>216</td>
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<tr>
<td>Tumor grade</td>
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<td></td>
</tr>
<tr>
<td>Histologic grade I</td>
<td>91</td>
<td>78</td>
<td>170</td>
<td></td>
<td>98</td>
<td>93</td>
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<tr>
<td>Histologic grade II</td>
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<td>76</td>
<td>171</td>
<td></td>
<td>94</td>
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<td>Histologic grade III</td>
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<td>0.002</td>
<td>93</td>
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<td>192</td>
<td>0.002</td>
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<tr>
<td>Tumor hormonal status</td>
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<td></td>
</tr>
<tr>
<td>Positive estrogen receptor</td>
<td>88</td>
<td>74</td>
<td>188</td>
<td></td>
<td>96</td>
<td>87</td>
<td>216</td>
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<tr>
<td>Negative estrogen receptor</td>
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<td>188</td>
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<tr>
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<tr>
<td>Negative progesterone receptor</td>
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<td>71</td>
<td>185</td>
<td>0.03</td>
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<td>209</td>
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<td>61</td>
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<td>0.03</td>
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<td>96</td>
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<tr>
<td>Negative HER2 overexpression</td>
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<td>187</td>
<td></td>
<td>92</td>
<td>84</td>
<td>215</td>
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<tr>
<td>No systemic adjuvant treatment</td>
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<td>59</td>
<td>134</td>
<td>0.006</td>
<td>96</td>
<td>86</td>
<td>203</td>
<td>0.612</td>
</tr>
<tr>
<td>All systemic adjuvant treatments</td>
<td>86</td>
<td>74</td>
<td>191</td>
<td></td>
<td>94</td>
<td>86</td>
<td>219</td>
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<td>75</td>
<td>159</td>
<td></td>
<td>94</td>
<td>87</td>
<td>173</td>
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<tr>
<td>Chemo. with anthracyclines</td>
<td>85</td>
<td>75</td>
<td>194</td>
<td></td>
<td>94</td>
<td>86</td>
<td>218</td>
<td></td>
</tr>
<tr>
<td>CMF chemotherapy</td>
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<td>44</td>
<td>134</td>
<td></td>
<td>95</td>
<td>90</td>
<td>220</td>
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<tr>
<td>Other chemo. schedules</td>
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<td>75</td>
<td>102</td>
<td></td>
<td>96</td>
<td>96</td>
<td>123</td>
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</tr>
</tbody>
</table>

RFS, relapse-free survival; BCSS, breast cancer-specific survival; CMF, cyclophosphamide, methotrexate and 5-fluorouracil.

**Discussion**

NNBC patients who have fewer than six nodes examined during axillary lymphadenectomy have a worse outcome with a greater risk of relapse and a shorter BCSS. Other adverse prognostic factors determined were age younger than 36 years, tumor size greater than 2 cm, tumor grade III, infiltrating ductal carcinoma (compared with other histological types) and negative hormonal receptors.
There is debate about the need for axillary lymphadenectomy and its optimum extent partly because it is associated with morbidity. Hack and colleagues [26] found that approximately 70% of patients who underwent lymphadenectomy had arm or shoulder pain, weakness, numbness or reduced mobility.

Consequently, there is evidence that the use of ALND is declining in the USA [27] and also that its omission may even be associated with poorer outcomes [11, 17, 28, 29]. Strategies for obtaining prognostic information without an ALND are being increasingly used. Sentinel node biopsy, when performed by experienced surgeons, has a high accuracy rate: Krag et al. [20] reported an accuracy of 97% in a series of 443 patients. However, the false-negative rates for the 11 surgeons in this study varied from 0% to 28.6%. Data demonstrate that patients do obtain benefit in terms of post-operative morbidity from avoiding complete axillary dissection [30]. However, there are no conclusive long-term data yet that reliably demonstrate the equivalence of patients’ outcome measures with sentinel lymph node biopsy versus axillary dissection. Despite this, sentinel lymph node biopsy has become a widely used procedure in Europe and the USA. However, a significant number of women with clinically negative axillae continue to undergo ALND and the results of our study and those of other trials examining the optimal number of resected lymph nodes at axillary dissection for staging purposes remain important.

Axelsson et al. [6] found a highly significant correlation between the number of nodes examined and axillary recurrence-free survival, overall recurrence-free survival and overall survival. Sosa [7] and Sommer [17], who recommended an examination of 16 nodes to ensure a high level of confidence that the nodes were negative, found similar results. Weir et al. [10] evaluated pathologically node-negative patients in two groups: those who did not receive systemic therapy and those who did. In the group that did not receive adjuvant treatment, patients with fewer nodes removed had significantly higher rates of regional recurrence compared with those who had more nodes removed. This effect was not seen in patients who received systemic therapy, suggesting that the poorer prognosis associated with examination of fewer lymph nodes may be counterbalanced by the use of adjuvant systemic therapy. In our study, we did not reach the same conclusion as Weir et al. because we did not segregate our patients on the basis of whether or not they received systemic therapy [most of our patients (89%) received adjuvant systemic therapy]. In our study among all patients who received adjuvant systemic therapy, RFS was significantly longer in comparison with untreated patients (P = 0.006, see Table 2) while BCSS rates were statistically similar in the two groups (P = 0.612, see Table 2). Since chemotherapy was administered to those patients with breast tumors possessing adverse prognostic factors, these data can be inferred to provide indirect evidence that adjuvant therapy was beneficial among treated patients.

When only a few nodes are found in the surgical specimen, it may be the result of an inadequate dissection, because nodes were not found at gross pathologic examination, or because only a few nodes were actually present due to anatomic variation. Petrik et al. [15] demonstrated a significant variation in the number of lymph nodes examined and an association between that variation and several patient, surgeon and hospital-related factors. In our study, the pathologic specimens were all submitted to a single hospital. Also, in this study, pathologic evaluation of lymph nodes did not routinely include immunohistochemical analysis. It is well known that more detailed evaluation of lymph nodes with immunohistochemistry...
Table 3. Statistically significant variables in Cox regression analyses for RFS and BCSS

<table>
<thead>
<tr>
<th>Variable</th>
<th>RFS HR (C.I. 95%)</th>
<th>BCSS HR (C.I. 95%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fewer than six lymph nodes examined</td>
<td>1.44 (1.03–2.00)</td>
<td>1.87 (1.20–2.91)</td>
<td>0.029</td>
</tr>
<tr>
<td>Patient younger than 36 years</td>
<td>2.39 (1.60–3.57)</td>
<td>1.69 (1.15–2.49)</td>
<td>0.000</td>
</tr>
<tr>
<td>Tumor larger than 20 mm</td>
<td>1.36 (1.06–1.75)</td>
<td>1.44 (1.07–1.95)</td>
<td>0.015</td>
</tr>
<tr>
<td>Infiltrating ductal carcinoma</td>
<td>1.56 (1.10–2.21)</td>
<td>1.73 (1.15–2.60)</td>
<td>0.000</td>
</tr>
<tr>
<td>Tumor histologic grade III</td>
<td>1.74 (1.14–2.66)</td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>Negative progesterone receptor status</td>
<td>1.44 (1.07–1.95)</td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>No administration of adjuvant systemic therapy</td>
<td>1.93 (1.34–2.76)</td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>Fewer than six examined nodes</td>
<td>1.87 (1.20–2.91)</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Tumor larger than 20 mm</td>
<td>1.69 (1.15–2.49)</td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>Negative progesterone receptor status</td>
<td>1.73 (1.15–2.60)</td>
<td></td>
<td>0.005</td>
</tr>
</tbody>
</table>

RFS, relapse-free survival; BCSS, breast cancer-specific survival; HR, hazard ratio.

will identify tumor cells missed on routine histological assessment and result in upstaging. The significance of these missed micrometastases, however, remains unclear [31]. In our institution, 14% of patients with NNBC had fewer than six lymph nodes examined, a statistic that has to be improved because the adequacy of axillary dissection is the only variable that can be modified among those factors which may account for a limited number of lymph nodes detected in the surgical specimen (specimen handling, pathologic examination and surgical technique).

In conclusion, fewer than six examined lymph nodes following axillary dissection in NNBC patients were associated with a worse outcome, possibly due to understaging. Nodal status is an important determinant of adjuvant chemotherapy use, and understaged patients who could benefit from the administration of chemotherapy may not receive appropriate systemic therapy. The examination of fewer than six lymph nodes at axillary dissection should be considered an adverse prognostic factor in clinical practice, in conjunction with other established clinopathologic factors, when considering a patient for adjuvant systemic therapy.

acknowledgements

We thank all the staff of the Department of Oncology and Hematology, Clinic Hospital, Valencia, Spain.

references


