Role of endocrine responsiveness and adjuvant therapy in very young women (below 35 years) with operable breast cancer and node negative disease

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Background: There is limited knowledge about prognosis, and treatment effects in young women with node-negative disease.

Patients and Methods: We evaluated biological features, treatment recommendations and prognosis for 841 premenopausal patients with pT1-3, pN0 and M0, operated from 1997 to 2001.

Results: Patients below 35 years (101, 12%) were more likely to have tumors > 2 cm (35.6% versus 24.2%, P = 0.002), grade 3 (48.5% versus 31.9%, P = 0.009) and with elevated Ki-67 expression (62.4% versus 50.7%, P = 0.002). At the multivariate analysis a statistically significant difference in disease-free survival (DFS, HR 4.44; 95% CI 2.53 to 7.78, P < 0.0001), risk of distant metastases (DDFS) (HR 3.23; 95% CI 1.32 to 7.94, P = 0.011) and overall survival (OS) (HR 2.89; 95% CI 1.06 to 7.87, P = 0.038) was observed for younger versus older patients and in the subgroup with endocrine responsive tumors (DFS, HR 5.17, 95% CI 2.72–9.83, P < 0.0001; DDFS, 3.76, 95% CI 1.33–10.6, P = 0.013; OS, 4.71, 95% CI 1.09–20.4, P = 0.039).

Conclusions: Compared with less young, very young patients with endocrine responsive and node-negative breast cancer have a worse prognosis. Tailored treatments should be explored in this cohort of patients.

Key words: breast cancer, prognostic features, very young women, endocrine responsiveness

Introduction

About 2% of the patients with breast cancer are less than 35 years old at diagnosis [1]. Breast cancer at a young age has been reported to pursue a more aggressive clinical course and to be associated with a more unfavorable prognosis compared with the disease in older patients [1–5].

Chemotherapy seems easier to offer (in terms of acceptance) to the younger patients because of its shorter duration and the lesser degree of long-term effects on endocrine functions. Typically, young patients receive adjuvant chemotherapy, and in many countries, clinicians have been reluctant to employ ovarian ablation or other endocrine treatment [5], although retrospective analyses suggest that the endocrine effects of chemotherapy alone are insufficient for the younger patients with endocrine-responsive breast cancer [6]. Endocrine therapies appear to be an essential component of an effective adjuvant therapy program [6]. Whether use of ‘optimal’ endocrine therapy (e.g. ovarian function suppression plus tamoxifen) may be sufficient for these patients is a hypothesis that has not been tested adequately.

Data on treatment effects are largely dependent upon older series, collected in several years, with endocrine therapies not adequately tested, and with extrapolation of data from older age cohorts. Moreover retrospective analyses focused on node positive disease or on both node-positive and node-negative disease [7], but in the past studies uncommonly focused on prognosis and adjuvant treatment in very young patients with node-negative breast cancer [8], a lower risk population where tailored therapies are of crucial importance.

The aim of this study was to investigate the most recently available details of biological characteristics and prognosis of very young patients (<35 years of age) with operable breast cancer and node negative disease treated with tailored adjuvant therapy.

Patients and methods

We prospectively collected information on all consecutive breast cancer patients operated at the European Institute of Oncology (IEO) between...
April 1997 and December 2001. Data on the patient’s medical history, concurrent diseases, surgery, pathological evaluation, and results of staging procedures (blood chemistry, hematological values, bone scan, chest film and upper abdominal ultrasound examination) were required. Pathological assessment included evaluation of the primary tumor size, histological type and of lymph nodes status including a sentinel node biopsy [9], when applicable. Tumor grade was evaluated according to Elston and Ellis [10] and peritumoral vascular invasion (PVI) was assessed according to Rosen [11]. Estrogen (ER) and progesterone receptor (PgR) status, Ki-67 labeling index (assessed with the MIB 1 monoclonal antibody), and HER2/neu over-expression (routinely performed since 1999) were evaluated immunohistochemically as previously reported [12]. The threshold for ER and PgR positivity was 1% and for Mib1 positivity 20%, as previously published [12]. The threshold for ER and PgR was based on published data indicating a different pattern of outcome according to the degree of potential endocrine responsiveness [13, 14].

Data were entered by surgeons into a ‘user-friendly’ database designed with Microsoft Access® with internal quality control. The database was then used for an interdisciplinary discussion among surgeons, medical and radiation oncologists and pathologists.

statistical analysis
The Mantel-Haenszel Chi-squared test for trend was used to assess the association between ordinal variables. The primary endpoints were disease-free survival (DFS) and overall survival (OS). DFS was defined as the length of time from the date of surgery to any relapse (including ipsilateral breast recurrence), the appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. OS was determined as the time from surgery until the date of death (from any cause) or the date of last follow-up. Multivariate Cox proportional hazard regression analysis was used to assess the independent prognostic significance of various clinical and histopathological characteristics of the tumor on survival. Factors included in multiple regression analyses included tumor diameter, ER and PgR expression, Ki-67 expression, vascular invasion, grade, histotype. For the subgroup of patients with endocrine responsive disease endocrine therapy was also introduced.

treatment received
All patients received adequate local treatment (breast conserving surgery or total mastectomy) plus axillary sentinel lymph node biopsy (SLNB) or complete axillary dissection. SLNB was followed by axillary dissection only if the sentinel node contained metastases or minimal node involvement. The SLN was identified and isolated using a gamma probe as a guide as previously published [15].

Postoperative breast irradiation (RT) was proposed to all the patients that received breast-conserving surgery [16]. Systemic adjuvant therapy was recommended according to St. Gallen’s treatment guidelines [16, 17]. For patients with endocrine responsive disease, adjuvant endocrine therapy alone was indicated (the combination of tamoxifen for 5 years plus LH-RH analogue for a minimum of 2 years) [12]. In patients at higher risk (i.e. occurrence of peritumoral vascular invasion, younger age, large tumors) and/or with features of uncertain endocrine responsiveness (e.g. low levels of ER positivity, lack of PgR expression, overexpression of HER2/neu, and increased proliferation markers, [18]), chemotherapy was added. Anthracycline containing chemotherapy was considered as the first option in patients with higher risk (i.e. AC, adriamycin and cyclophosphamide, for four courses [19]; in case of comorbidities or patients preferences classical CMF (oral cyclophosphamide, methotrexate and fluorouracil) for a duration of three to six courses was considered [20]. In case of endocrine non-responsive disease 6 months of chemotherapy was commonly indicated (classical CMF for six courses or AC for four courses followed by classical CMF for three courses [14] according to the degree of the patient risk).

results
A total of 4231 patients with breast cancer were referred to the interdisciplinary evaluation and their data were included in the database. We selected 979 premenopausal patients aged ≤50 years (22.4%) and node negative disease. Premenopausal status was defined as having normal menstrual period or in case of doubt with premenopausal LH, FSH, and E2 levels.

We subsequently excluded 138 patients, 68 that presented with neoadjuvant therapy, 17 previous other primary, 25 bilateral tumors, 16 recurrent or metastatic tumors, and 12 non-invasive breast cancers. A total of 841 patients were thus included in the analysis. 101 (12%) were ‘very young’ and 740 (88%) were classified ‘less young’.

The number of patients evaluable for each biological feature is given in Table 1. Seven patients were not evaluable for endocrine responsiveness (two due to small tumor dimension (pT1mic) and five due to biological features performed elsewhere with no further invasive breast cancer at the final surgery performed at the EIO).

In the ‘very young’ group, when compared with the ‘less young’ patients, there were higher percentages of tumors classified ER (41.6% versus 17.4%; P < 0.0001) and PgR (47.5% versus 23.2%; P < 0.001) absent, larger than 2 cm (35.6% versus 24.2%; P < 0.002), of high grade (48.5% versus 31.9%; P = 0.009) and with elevated Ki-67 labeling index (62.4% versus 50.7%; P = 0.002).

surgical treatment
14 patients (14.9%) in the very young group and 135 (18.2%) in the less young group underwent total mastectomy as the primary treatment and 86 (85.1%) in the very young group and 605 (81.8%) in the less young group (P = 0.49) had breast-conserving surgery. SLNB was performed in 45 patients (44.5%) in the very young group and 358 (48.4%) in the less young group (P = 0.52).

adjuvant treatment
As shown in Table 2, in endocrine unresponsive disease chemotherapy was indicated in 37 (88.1%) patients in the very young group and in 116 (89.9%) patients in the less young group (P = 0.77).

In endocrine responsive disease (ER > 0% of the cells) chemotherapy was indicated in 39 (67.2%) of very young patients compared with 268 (44.3%) of older patients (P = 0.0009); whereas endocrine therapy was proposed to 54 (93.1%) and 581 (96.0%) in the very young and less young groups respectively (P = 0.30). Refusal of endocrine therapy was slightly more frequent in very young (5/58; 8.6%) than in less young patients (34/605; 5.6%), but the difference was not statistically significant (P = 0.37).

As showed in Table 2, 18 patients with ER-absent tumors did not receive a chemotherapy proposal (pT1mic or pT1a disease seven patients; favorable histology nine patients; PgR positive disease and therefore candidate to endocrine therapy, two patients). Endocrine therapy was proposed to 15 patients with ER-absent tumors (PgR-positive disease eight patients; physician or patient preferences seven patients).
Median follow-up for this cohort of patients was 45.6 months for DFS and 53.9 months for OS. The cohort contributed to 3181 person-years of observation for DFS and 3789 for OS. Five-year DFS for very young patients and older patients with node negative disease, were 70% (95% CI 58% to 83%) versus 91% (95% CI 89% to 94%) respectively, log-rank \( P < 0.0001 \). Five-year OS were 93% (95% CI 86% to 99%) versus 98%, 95% CI 97% to 99% respectively, log-rank \( P = 0.0007 \) (Figure 1a–b).

For endocrine unresponsive disease (ER = 0% of the cells), five-year DFS for very young patients and older patients with node negative disease, were 74% (95% CI 55% to 94%) versus 94% (95% CI 90% to 98%) respectively, log-rank \( P = 0.0196 \). Five-year OS were 85% (95% CI 71% to 99%) versus 95% (95% CI 91% to 99%) respectively, log-rank \( P = 0.24 \) (Table 3).

For endocrine responsive disease (ER \( \geq 1\% \)), five-year DFS for very young patients and older patients with node negative disease, were 68% (95% CI 53% to 84%) versus 91% (95% CI 88% to 94%) respectively, log-rank \( P < 0.0001 \). Five-year OS were 98% (95% CI 95% to 100%) versus 99% (95% CI 98% to 100%) respectively, log-rank \( P = 0.0081 \) (Figure 1e–f).

Table 3 presents the rate and type of event in the 663 patients with endocrine responsive tumor, according to age and hormonotherapy. The very young patients for whom hormonotherapy was not proposed, or who refused hormonotherapy experienced four times more events than those who complied with therapy (20.7 events per 100 women per year versus 5.2/100/year). This excess was smaller in less young patients (3.3/100/year versus 1.4/100/year) (Table 3).

multivariate analysis
A statistically significant difference in DFS, risk of distant metastases and OS was observed at the multivariate analysis, for younger patients versus older patients (HR = 4.44; 95% CI 2.53 to 7.78; \( P < 0.0001 \) for DFS; HR = 3.23; 95% CI 1.32 to 7.94; \( P = 0.011 \) for distant metastases; HR = 2.89; 95% CI 1.06 to 7.87; \( P = 0.038 \) for OS) (Table 4). An increased risk was...
observed in particular for patients with endocrine responsive disease (ER ≥1%) (HR = 5.17, 95% CI 2.72 to 9.83; \(P<0.0001\) for DFS). Adjuvant endocrine therapy significantly reduced the risk of relapse in patients with endocrine responsive disease (HR = 0.35; 95% CI 0.18 to 0.70; \(P=0.0003\) for DFS).

In an exploratory analysis, the magnitude of detrimental effect for younger age was particularly large in the group of patients with endocrine responsive disease that did not receive or reduced the proposed treatment (HR 7.77; 95% CI 1.98 to 30.6, \(P=0.0033\) for DFS). A large effect for endocrine therapy in very young patients was observed (HR = 0.20; 95% CI 0.05 to 0.74; \(P=0.016\) for DFS), but no statistically significant interaction between age and effect of endocrine therapy was observed (\(p\) for interaction 0.21).

In endocrine unresponsive disease a statistically significant difference in DFS but not OS was observed for very young patients versus older patients in univariate analysis (HR = 3.26, 95% CI 1.14 to 9.33, \(P<0.0196\) for DFS; HR = 2.12, 95% CI 0.60 to 7.51; \(P=0.24\) for OS). The association disappeared in multivariate analysis.

**discussion**

The results of the present study indicate that ‘very young’ patients with operable breast cancer and node negative disease presented more frequently with tumors with poor prognostic features like endocrine non-responsive disease, high grade, and high proliferating fraction than ‘less young’ premenopausal...
patients. These results confirm in a selected population considered to be at lower risk (node-negative disease), previously reported data indicating that breast cancer, which develops at a young age, is different from that arising in older premenopausal patients [1, 5].

Beside the feature of a more aggressive disease presentation which reflects on patients outcome, the results of the present study support the issue that the age 35, which according to previously published data [7] was chosen as threshold between the two age groups, led to identification of groups which require adjuvant tailored therapies. In fact, younger age was significantly correlated with worse DFS, DDFS and OS, with a detrimental effect larger in the group of patients with endocrine responsive disease. This study provides useful insights

Table 3. Performed treatment and events in 663 patients with endocrine responsive node negative breast cancer according to age at diagnosis and treatment

<table>
<thead>
<tr>
<th>Hormonotherapy in women with ER+ tumors</th>
<th>No. of patients</th>
<th>Person years</th>
<th>No. of events</th>
<th>Event rate per 100/year</th>
<th>Type of events Local relapse</th>
<th>Distant metast.</th>
<th>Contra-lateral</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>663</td>
<td></td>
<td>34</td>
<td>1.6</td>
<td>10</td>
<td>17</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td>Performed</td>
<td>515</td>
<td>2068</td>
<td>34</td>
<td>4.5</td>
<td>2</td>
<td>2</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Not proposed</td>
<td>28</td>
<td>111</td>
<td>5</td>
<td>3.7</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Refused</td>
<td>39</td>
<td>161</td>
<td>9</td>
<td>5.1</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Not proposed/or refused</td>
<td>67</td>
<td>272</td>
<td>14</td>
<td>3.1</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>81</td>
<td>205</td>
<td>3</td>
<td>1.5</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
</tbody>
</table>

Age <35                                  | 58              |              | 8             | 5.2                    | 4                          | 2              | –             | –     |
| Performed                              | 41              | 154          | 8             | 14.3                   | –                          | 1              | –             | 1     |
| Not proposed                           | 4               | 14           | 2             | 26.7                   | 2                          | 2              | –             | –     |
| Refused                                | 5               | 15           | 4             | 20.7                   | 2                          | 1              | 2             | 1     |
| Not proposed/or refused                | 9               | 29           | 6             | 3.3                    | 1                          | 4              | –             | –     |
| Unknown                                | 8               | 7            | 0             | –                      | –                          | –              | –             | –     |

Age ≥35                                  | 605             |              | 26            | 1.4                    | 6                          | 13             | 7             | –     |
| Performed                              | 474             | 1914         | 26            | 3.1                    | 2                          | 1              | –             | –     |
| Not proposed                           | 24              | 97           | 3             | 4.1                    | 1                          | 4              | –             | –     |
| Refused                                | 34              | 146          | 5             | 26.7                   | 2                          | 4              | –             | –     |
| Not proposed/or refused                | 58              | 243          | 8             | 3.3                    | 3                          | 5              | –             | –     |
| Unknown                                | 73              | 198          | 3             | 1.5                    | 1                          | –              | 1             | 1     |

Table 4. Multivariate analysis: prognostic value of selected tumor characteristics on disease outcomes

<table>
<thead>
<tr>
<th>Tumour characteristics</th>
<th>Distant metastasis HR (95% CI)</th>
<th>P-value</th>
<th>Disease-free survival HR (95% CI)</th>
<th>P-value</th>
<th>Overall survival HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL WOMEN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;35 versus ≥35</td>
<td>3.23 (1.32–7.94)</td>
<td>0.011</td>
<td>4.44 (2.53–7.78)</td>
<td>&lt;.0001</td>
<td>2.89 (1.06–7.87)</td>
<td>0.038</td>
</tr>
<tr>
<td>ER/PgR Absent versus present</td>
<td>0.82 (0.31–2.13)</td>
<td>0.679</td>
<td>0.71 (0.37–1.36)</td>
<td>0.303</td>
<td>3.79 (1.31–10.9)</td>
<td>0.014</td>
</tr>
<tr>
<td>Ki-67 &gt;20% versus &lt;20%</td>
<td>2.17 (0.83–5.71)</td>
<td>0.116</td>
<td>1.83 (1.02–3.31)</td>
<td>0.044</td>
<td>0.76 (0.24–2.41)</td>
<td>0.640</td>
</tr>
<tr>
<td>IVP Present versus absent</td>
<td>3.56 (1.60–7.96)</td>
<td>0.002</td>
<td>2.06 (1.18–3.59)</td>
<td>0.011</td>
<td>1.95 (0.68–5.38)</td>
<td>0.214</td>
</tr>
<tr>
<td>Diameter &gt;2 cm versus ≤2 cm</td>
<td>2.76 (1.26–6.03)</td>
<td>0.011</td>
<td>1.94 (1.16–3.23)</td>
<td>0.012</td>
<td>3.06 (1.19–7.89)</td>
<td>0.021</td>
</tr>
<tr>
<td>Her-2 +++ versus other</td>
<td>1.70 (0.66–4.41)</td>
<td>0.275</td>
<td>1.24 (0.61–2.55)</td>
<td>0.555</td>
<td>0.42 (0.05–3.47)</td>
<td>0.421</td>
</tr>
<tr>
<td>ER+ Age &lt;35 versus ≥35</td>
<td>3.76 (1.33–10.6)</td>
<td>0.013</td>
<td>5.17 (2.72–9.83)</td>
<td>&lt;.0001</td>
<td>4.71 (1.09–20.4)</td>
<td>0.039</td>
</tr>
<tr>
<td>Ki-67 &gt;20% versus &lt;20%</td>
<td>2.60 (0.92–7.36)</td>
<td>0.073</td>
<td>1.88 (1.02–3.47)</td>
<td>0.045</td>
<td>0.73 (0.17–3.23)</td>
<td>0.683</td>
</tr>
<tr>
<td>IVP Present versus absent</td>
<td>2.84 (1.12–7.18)</td>
<td>0.027</td>
<td>1.78 (0.96–3.32)</td>
<td>0.070</td>
<td>4.57 (1.11–18.9)</td>
<td>0.036</td>
</tr>
<tr>
<td>Diameter &gt;2 cm versus ≤2 cm</td>
<td>2.23 (0.92–5.42)</td>
<td>0.077</td>
<td>1.63 (0.90–2.96)</td>
<td>0.109</td>
<td>1.42 (0.30–6.64)</td>
<td>0.659</td>
</tr>
<tr>
<td>Her-2 +++ versus other</td>
<td>1.63 (0.56–4.74)</td>
<td>0.372</td>
<td>1.52 (0.68–3.44)</td>
<td>0.310</td>
<td>1.54 (0.13–18.0)</td>
<td>0.713</td>
</tr>
<tr>
<td>Hormonotherapy Yes versus No</td>
<td>0.57 (0.18–1.86)</td>
<td>0.354</td>
<td>0.37 (0.19–0.74)</td>
<td>0.005</td>
<td>0.31 (0.06–1.54)</td>
<td>0.153</td>
</tr>
<tr>
<td>ER+ Age &lt;35 versus ≥35</td>
<td>2.97 (0.46–19.4)</td>
<td>0.255</td>
<td>2.77 (0.88–8.80)</td>
<td>0.083</td>
<td>1.79 (0.45–7.12)</td>
<td>0.408</td>
</tr>
<tr>
<td>Ki-67 &gt;20% versus &lt;20%</td>
<td>0.27 (0.02–3.65)</td>
<td>0.325</td>
<td>1.50 (0.18–12.8)</td>
<td>0.709</td>
<td>1.35 (0.16–11.5)</td>
<td>0.785</td>
</tr>
<tr>
<td>IVP Present versus absent</td>
<td>8.95 (1.40–57.3)</td>
<td>0.021</td>
<td>2.37 (0.62–9.03)</td>
<td>0.205</td>
<td>0.63 (0.08–5.14)</td>
<td>0.665</td>
</tr>
<tr>
<td>Diameter &gt;2 cm versus ≤2 cm</td>
<td>3.97 (0.59–26.7)</td>
<td>0.157</td>
<td>1.99 (0.64–6.20)</td>
<td>0.237</td>
<td>4.26 (1.07–16.9)</td>
<td>0.039</td>
</tr>
<tr>
<td>Her-2 +++ versus other</td>
<td>1.51 (0.19–11.8)</td>
<td>0.693</td>
<td>0.63 (0.13–3.12)</td>
<td>0.573</td>
<td>0.00 (0.00–.)</td>
<td>0.994</td>
</tr>
</tbody>
</table>
amenorrhea was associated with an increased risk of relapse in patients. The failure to achieve chemotherapy-induced amenorrhea 

Factors influencing acceptance of endocrine therapies by very young patients are crucial for very young patients. 

In the present study, at variance with the above analysis, patients were candidate to endocrine therapy. In the very young population with endocrine-responsive disease, 93% of the patients were prescribed adjuvant endocrine therapy. Patients with endocrine-responsive disease aged <35 years overall had a poorer outcome if compared with older patients with a large detrimental effect of age observed in those patients that did not comply with the proposed endocrine treatment (HR 7.77; 95% CI 1.98 to 30.6, \( P = 0.0033 \) for DFS, Figure 2).

Although the latter results were registered in an exploratory analysis, and no statistically significant interaction between age and effect of endocrine therapy was observed (possibly due to the small number of patients), they suggest that endocrine therapies are crucial for very young patients. Factors influencing acceptance of endocrine therapies by very young women are however complex, involving issues such as induced menopausal symptoms, and issues of sexual functioning and family planning [21, 22].

Data in the literature support a role for ovarian function suppression in the adjuvant program of pre-menopausal patients. The failure to achieve chemotherapy-induced amenorrhea was associated with an increased risk of relapse among pre-menopausal patients with ER-positive tumors in a retrospective analysis of IBCSG Trials I, II, V and VI [23].

The present study, focusing on a node negative population, differs from the mentioned trials in the methodology used for the assessment of endocrine responsiveness. In the trials described above, analyses were performed with different methods (biochemical and immunohistochemical) based on a so-called ‘receptor-negative grouping’, which combines receptor-absent disease with that expressing low receptor levels. In the present study, endocrine nonresponsive disease was defined through immunohistochemistry as steroid hormone receptor absent tumor. Some clinical studies [27] and gene

![Figure 2](Image)
expression profiling [28] already provide empirical data that receptor-absent breast cancer is a distinct entity from that with even low levels of receptor expression.

In conclusion, the results of the present study indicate that, within the first years, the younger patients with breast cancer have a dire prognosis with a statistically significant detrimental effect of age for endocrine-responsive disease. Moreover, on an exploratory analysis, a particularly poor outcome was observed for very young patients who did not comply with the proposed endocrine treatment. Despite the impressive magnitude of the observed effect associated with endocrine responsiveness in very young patients and the compelling biological explanations for this effect, the potential for bias still exists due to the retrospective nature of the evaluation. Further studies designed to confirm the importance of endocrine therapies in very young patients with hormone-responsive disease are required because substantial evidence exists that the current approaches are sub optimal.

references