INTRODUCTION

The staging of axillary lymph node invasion of breast cancer is considered to be the single most important factor.(1,2) Therefore, axillary staging is a mainstay of surgical therapy for invasive breast disease.(3,4) In the era prior to determination of sentinel lymph node (NLS), axillary lymph dissection was performed systematically.(4,5)

Established breast cancer prognostic factors - those that determine natural history of breast cancer- include axillary nodal status, tumour volume, histological grade, hormone receptor status, HER-2 expression and presence of lymphovascular invasion. These factors influence the decision on the application of adjuvant systemic therapy.

In contrast, predictive markers such as: estrogen receptor expression (RF), alpha, progesterone receptor (PR) and HER2 protein, are powerful tools to select the right type of therapy.

In this molecular age, it is important to reflect on the continuing importance of classic histopathology. One such feature is the identification of lympho-vascular invasion. Bags for important prognostic what was suggested in 2007 consensus conference in St. Gallen (2) where extensive lympho-vascular invasion was identified as a factor to identify women at moderate risk factor in contrast with a low relapse. This classic histopathology analysis has been amplified by immunohistochemistry analysis (IHC).(6,7)

Preoperative chemotherapy has become the standard of care for inoperable locally advanced breast cancer, and the role of preoperative chemotherapy for operable breast cancer evolved with three proposed theoretical advantages of preoperative chemotherapy.(8,9,10,11)

The first is preoperative tumour regression, allowing breast conservation therapy, for that category of patients which would have required mastectomy.(12,13,14,15,16)

The second is the treatment of micrometastases without delay postoperative recovery.(17,18)

The third is the ability to evaluate the response to chemotherapy administered in vivo.(19,20,21)

Several studies have consistently shown that lympho-vascular invasion is an adverse prognostic factor for recurrence and survival in node-negative patients in combination with other risk factors such as tumour grade, volume and receptor status.(22)

B. Ejersten et al (23) reported a comprehensive analysis of the prognostic value of lympho-vascular invasion in breast tumours from 15%, 59 women registered in to the Danish Breast Cancer Group between 1996 to 2002, noting the presence of lympho-vascular invasion, in only 15% of tumours.

Intramammary lymph nodes represent a potential extraaxillary site of regional breast cancer metastasis, which are defined as lymph nodes surrounding by breast parenchyma and can be located anywhere in the breast.

PURPOSE

The purpose of this study was to determine the prognostic information gained through clear dissection of axillary lymph nodes that were altered by preoperative
chemotherapy in patients with stage T3N0 breast cancer treated in the 1st Surgical Clinic of Sibiu between 2002 and 2008.

**MATERIALS AND METHODS**

From this study, patients who received preoperative radiotherapy were excluded and the remaining 95 patients received neoadjuvant chemotherapy combined according to the protocol during the interval studied.

Fifty-five patients received both: preoperative chemotherapy (preoperative CT) and postoperative chemotherapy (postoperative CT) and 40 patients received postoperative chemotherapy only (postoperative CT).

All patients with preoperative chemotherapy, tumour biopsies were performed with surgical excision biopsy or fine needle aspiration or biopsy with cylindrical trocar.

All patients underwent staging techniques including history, physical examination, blood analysis, abdominal mammography, chest X-ray, abdominal CT or ultra-sonography.

None of these patients had distant metastatic disease, and none of them developed distant metastasis or clinically positive lymph node during preoperative chemotherapy.

The clinical response to preoperative CT was defined as partial response (> 50% reduction in the two largest dimensions of the breast mass), stable disease (breast mass reduction <50%) and complete response (complete resolution of breast mass).

During the current study, one patient has progression of her primary tumour on preoperative CT, and received preoperative radiotherapy, therefore this case is not included in the current study.

After preoperative chemotherapy and complete response, or a response >50%, and peripheral tumour, large mammary seckecotomy and axillary lymph node dissection, or modified radical mastectomy was indicated, and in all cases with response <50% the modified radical mastectomy was systematically indicated.

The follow-up time was 5 years (1-13 years).

Disease specific survival was calculated from the date of diagnosis and disease free survival was calculated from the date of surgery, using the method of Kaplan and Meier and tag-rank analysis was used for univariate comparison, multivariate regression model was applied to calculate the proportional hazard of events.

Differences between groups were considered statistically significant at p <0.5.

### RESULTS

The list of patients and tumour characteristics for the pre- and postoperatively CT are shown in table no. 1.

**Table no. 1. Tumour characteristics for the pre- and postoperatively CT**

<table>
<thead>
<tr>
<th>Date</th>
<th>CT preop</th>
<th>CT postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Age (mean years)</td>
<td>50 (25-66)</td>
<td>49 (24-76)</td>
</tr>
<tr>
<td>Initial tumour volume (mean cm)</td>
<td>6 (5-12.5)</td>
<td>6 (5-10)</td>
</tr>
<tr>
<td>Family history</td>
<td>10 (17%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Histology</td>
<td>cc. invasive ductal</td>
<td>cc. invasive lobular</td>
</tr>
<tr>
<td></td>
<td>45 (83%)</td>
<td>23 (58%)</td>
</tr>
<tr>
<td></td>
<td>7 (11%)</td>
<td>8 (18%)</td>
</tr>
<tr>
<td></td>
<td>noninvasive</td>
<td>noninvasive</td>
</tr>
<tr>
<td></td>
<td>3 (4%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td></td>
<td>other</td>
<td>other</td>
</tr>
<tr>
<td></td>
<td>7 (18%)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Estrogen receptor status</td>
<td>negative</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>21 (48%)</td>
<td>25 (45%)</td>
</tr>
<tr>
<td></td>
<td>13 (32%)</td>
<td>21 (53%)</td>
</tr>
<tr>
<td></td>
<td>not</td>
<td>not</td>
</tr>
<tr>
<td></td>
<td>9 (17%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>Progesterone receptor status</td>
<td>negative</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>28 (51%)</td>
<td>11 (19%)</td>
</tr>
<tr>
<td></td>
<td>10 (24%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td></td>
<td>not</td>
<td>not</td>
</tr>
<tr>
<td></td>
<td>16 (30%)</td>
<td>20 (53%)</td>
</tr>
</tbody>
</table>

Table no. 1 shows that there was no difference between the groups in patient characteristics or in most tumour characteristics.

Patients with preoperative CT showed the highest percentage progesterone receptor negative tumours (51% vs. 24% p = 0.3).

After preoperative CT 5 (8%) of the 55 patients had complete clinical response, 37 (68%) partial clinical response and 13 (25%) had a stable disease.

In the group with preoperative CT, 9 (15%) of patients underwent conservative breast surgery and two (3%) of the postoperative CT group underwent breast conservative surgery (p = 0.5).

The median tumour volume in the group with preoperative CT was lower (3 cm) compared with postoperative CT group (6 cm) p <0.1 (table no. 2), reflecting the primary tumour response in the preoperative CT cases.

The vascular/lymphatic invasion in preoperative CT group was lower (15%), compared to 47% of postoperative CT group (p <0.1), and the difference about extranod extension was 19% vs. 42% (p = 0.2).

In the group with preoperative CT average number of positive lymph nodes was 0 vs. 3 (p <0.1) and in preoperative CT group 64% of the patients had pathologically lymph node, and 5% of patients from the group postoperative CT has negative lymph nodes (p = 0.3).

**Table no. 2. Constants pathological cases with pre- and postoperative CT**

<table>
<thead>
<tr>
<th>Anat. pathological</th>
<th>CT preop n=55</th>
<th>CT postop n=40</th>
<th>Value p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour size (cm average)</td>
<td>4 (1-7.5)</td>
<td>7 (4.12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vacular-lymphatic invasion</td>
<td>9 (15%)</td>
<td>19 (47%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Extranodal extension</td>
<td>10 (19%)</td>
<td>16 (42%)</td>
<td>0.2</td>
</tr>
<tr>
<td>The average number of harvested NL</td>
<td>11</td>
<td>14</td>
<td>0.05</td>
</tr>
<tr>
<td>Nr. NL +</td>
<td>0 N+ 35 (64%) 1-3 N+ 13 (23%) 4-9 N+ 6 (6%) &gt;N+ 1 (2%)</td>
<td>3 (5%) 19 (47%) 10 (26%) 8 (21%)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

In 75% of patients with preoperative CT, there was observed the presence of residual tumour, 6% had microscopic tumour and 19% of cases had residual active tumours.

The majority of complete pathological responses were initially tumour estrogen receptor negative (p = 0.2) and anaplastic (p = 0.4).

Patients in groups pre- and post-operative CT did not showed significant difference in disease-free survival or disease-specific survival (table no. 3).

**Table no. 3. Difference in disease-free survival or disease-specific survival**

<table>
<thead>
<tr>
<th></th>
<th>Preop CT</th>
<th>Postop CT</th>
<th>Value p</th>
</tr>
</thead>
<tbody>
<tr>
<td>The percentage of disease-free survival (95% CI) for 5 years</td>
<td>66%</td>
<td>57%</td>
<td>0.37</td>
</tr>
<tr>
<td>Disease specific survival (95% CI) to 5 years</td>
<td>90%</td>
<td>81%</td>
<td>0.34</td>
</tr>
</tbody>
</table>

In the group with preoperative CT, by Cox regression analysis showed the presence of two predictors for both disease-free and disease-specific survival – the presence of extranodal extension (p <0.1) and the number of positive lymph nodes (N +) (p = 0.01).

In survival analysis Kaplan - Meier, for preoperative CT group the only factor predictive of disease-free survival was
the pathologic tumour response.

The axillary lymph node status confers a poor prognosis when persists after preoperative chemotherapy.

**DISCUSSIONS**

Axillary surgery is employed to control axillary nodal disease and to staging the tumour accurately in order to assess prognosis and possible benefit from systemic therapy. In the elderly there is little evidence of the benefit of adjuvant chemotherapy.(24,25)

Consequently, same authors believe that to stage the clinically uninvolved axilla with either a clearance or sampling may be unjustified and axillary surgery is undertaken less often in the elderly patients.(26)

However, adjuvant therapy other than chemotherapy may be based on staging information, such as administration of tarroxfen or radiotherapy.(25,27,28)

In addition omitting axillary surgery exposes the patients to a high risk of axillary recurrence if axillary disease is present.

Invasive lobular carcinoma of the breast is 4.9-15% of all invasive breast cancers, making it the most common histologic subtype after invasive ductal carcinoma, the incidence in this study was 11%.

In patients with clinically stage T3N0 carcinoma, the number of cases with N (-) of the axillary lymph node (no metastasis), was higher in cases who received both preoperative and postoperative (64%) suggesting the down staging effect of CT preoperative.

The present results are limited because the study is retrospective.

The study results show the down staging of N status at the axilla, of patients with stage T3N0.

In the study reported from Kuerer et al (21) 32% of patients with locally advanced breast cancers with clinically positive lymph node clinical at the first exams axillary tumour down staging (clinically, sonographically) after preoperative CT.

McGready et al, Schwartz et al (30,31), Singletary et al (32) also reported conversion to clinically invaded axillary lymph node to pathologically negative lymph node status in patients with locally advanced breast cancer benefit from preoperative chemotherapy. In the preoperative CT patients, with four or nine positive nodes, pathologically positive nodes invaded was associated with a worse evolution, because it is possible that this reflects the evident down staging in nodal status after preoperative CT.

In the present study, patients with preoperative CT and 4-9 positive (N+) lymph nodes may be more similar in term initial stage of the disease, cases of postoperative CT with 10 positive node, that the cases with postoperative CT cases with 4-9 positive nodes.

In our study, the pathological examination was performed by staining with hematoxylin classic - eosin, since the number of cases with IHC, HER2 determination is currently still limited. In the study of Kuerer and Colob (33) 10% of patients with preoperative CT and evaluation of lymph node with hematoxylin based - eosina were found to have accret nodal metastases, by step-sections and IHC staining of their lymph node, observations presented from others to.(34,35,36)

The more aggressive tumours, were those with estrogen receptor negativity and anaplastic tumours, with a higher risk for axillary metastatic dissemination, at initial clinically examination.

Machiavelli et al (37) have also reported a correlation between residual primary tumour after preoperative CT and the number of positive lymph nodes.

Similarly observations were presented by others to.(38-39) During the last decade, our understanding of the molecular alterations involved in breast cancer, and in metastatic tumours has significantly advanced.

Many of these molecular markers have been proposed as predictors of tumour biology and tumour sensitivity to chemotherapy.(40,41,42)

The role of sentinel lymph node (NLS) technology is an alternative to axillary lymph node dissection for the assessment of nodal status in patients with preoperative chemotherapy.

Multiple trials have documented that sentinel lymph node biopsy (NLS) reflect the state of the axilla.(43-45)

**CONCLUSIONS**

Status axillary lymph nodes provide useful prognostic information in patients with breast cancer stage T3 N0, even after down staging from preoperative chemotherapy.

The presence of pathologically positive lymph nodes after preoperative chemotherapy was associated with poor prognosis.

Patients with positive lymph node after chemotherapy represent a category with relative resistance to chemotherapy.

**REFERENCES**


42. Arnaout-Alkatain A, Narod SA, Sun PA, Marks AN. Significance of lymph vessel invasion identified by the endothelial lymphatic marker D2-40 in node negative breast cancer. Mod Pathol. 2007;20(2):183-191.

