Impact of Radical Surgery on Outcome in Locally Advanced Breast Cancer Patients Without Metastasis at the Time of Diagnosis

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Abstract. Background/Aim: In the era of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18FDG-PET/CT), more patients are being diagnosed with N3M0 disease. The objective of this study was to assess the prognostic impact of radical lymph node surgery (RLNS) in patients with locally advanced breast cancer classified as lymph node N3 disease according to the American Joint Committee on Cancer (AJCC) 2002 in whom there is no known distant metastasis and in the context of multimodal therapy. Patients and Methods: This was a two-Center retrospective study that included patients with breast cancer classified as N3M0 after 18FDG-PET/CT assessment. We reviewed the clinical characteristics, surgical treatment and oncological outcomes of those patients. Results: Thirty-nine patients fulfilled the inclusion criteria. Multimodal treatment included neo-adjuvant chemotherapy (n=34), adjuvant radiotherapy (n=53), adjuvant chemotherapy (n=18) or neo- or adjuvant hormone therapy (n=17). Surgical treatment was not homogeneous. Eight patients had undergone RLNS and 31 conventional axillary lymph node dissection (CD). There was no significant difference in median overall survival between the RLNS group and the CD group (32 months (28-36) vs. 49 months (42-56) respectively (p=0.25)). The overall recurrence rate was 23%. Out of the 8 patients who had undergone RLNS, three had relapsed (two with distant metastases and one local). Conclusion: RLNS was not proven to be beneficial in our study. In order to guide surgical management for these patients, PET/CT and magnetic resonance imaging (MRI) could be of interest, therefore a pilot study to improve reproducible surgical management would be of interest.

Since a long time, patients with locally advanced breast cancer (LABC) without distant metastases were thought to have a poor prognosis and have been treated palliatively. In 2001, Brito et al. demonstrated that prognosis of patients with multimodal treatment was significantly better than that seen in patients with visceral stage IV disease (1). They concluded that such patients should be treated with a curative multimodal approach rather than palliatively. The 2003 revision of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system reclassified these patients with M1 disease to a newly-created stage IIIIC category that encompasses patients with any T, N3 (pN3a, pN3b, pN3c) and M0 (2). This stage IIIC remained unchanged in the last revision of the AJCC in 2010 (3).

The use of “whole-body” 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18FDG-PET/CT) has recently become widespread for the initial staging of advanced breast cancer. Groheux et al. reported that 18FDG-PET/CT changed staging in 30.3% of 254 patients by detecting distant metastases or N3 disease (lymph node involvement in the Berg level 3 and/or in the supraclavicular area and/or in the internal mammary chain) (4). With this widespread use of PET/CT for initial staging, more patients with “asymptomatic” N3M0 breast cancer could be identified and benefit from extensive curative treatment.

To our knowledge, the prognostic impact of radical axillary lymph node dissection, as part of initial multimodal therapy, has not yet been studied in patients with stage IIIIC breast cancer. Chen et al. demonstrated a significant improvement in 5-year overall survival of patients in whom good control of metastatic nodes in the neck region was obtained, either by excisional biopsy or by total removal (5). Currently, there is no recommendation regarding the type of surgery to perform for patients with LABC and initial N3 disease.
The aim of the present study was to evaluate the prognostic impact of radical lymph node surgery (RLNS) as part of initial multimodal therapy in patients with LABC without distant metastasis (stage IIIC).

Patients and Methods

Patients and treatments. This was a retrospective study conducted in two breast cancer and oncologic surgery referral Centers (Gustave Roussy (GR) in Villejuif and Saint Louis Hospital in Paris). The research method in GR was performed on "Google Search IGR" using the following key words: "retro-pectoral, breast cancer and Berg level III." Twelve patients were found between 2000 and 2013. Patients with distant metastases (n=1), those undergoing treatment at the time of data collection (n=4) and those who had not been operated on due to refusal of care (n=1) were excluded. A total of 6 patients were identified at GR. We based our literature search on an article published in 2012 in the Journal of the National Cancer Institute “JNCI” by the Nuclear Medicine team of D. Groheux at Saint Louis Hospital (4). They prospectively analyzed the impact of PET/CT on the prognosis of breast cancer stages IIB and III between January 2006 and November 2011. The data, concerning 33 patients with the same characteristics as ours, were retrieved with the help of the Saint Louis team. PET/CT was systematically performed for a prospective study at St. Louis hospital, whereas the examination was decided in case of a high metastatic risk at GR.

The inclusion criteria in our study were all patients classified as having stage IIIC breast cancer (N3M0, according to the sixth edition of the AJCC) either clinically or by imaging (conventional imaging or PET/CT) and who required combined modality therapy comprising chemotherapy, surgery, radiotherapy and/or hormonal therapy. Data on patients’ clinical characteristics, details on the histologic types and the treatment patients had received in each center were collected from the hospital records. The chemotherapy drugs were different depending on the center and the date of treatment. Most patients had received neo-adjuvant chemotherapy (NAC).

The type of surgery was decided by the attending surgeon: either a radical axillary lymph node dissection defined as a dissection of the nodes at all three Berg levels with or without a supra-clavicular lymph node dissection (RLNS group) or a conventional axillary dissection defined as a dissection of the nodes at the first two Berg levels (CD group). A mastectomy was performed when the tumor was inflammatory or had not responded to NAC sufficiently to qualify for conservative treatment. The extent of radiotherapy was homogeneous in the two centers (chest wall, supra-clavicular area, internal mammary chain). Axillary irradiation was indicated in case of massive axillary extension at surgery.

Table I. Patients’ and tumor characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients n=39 (%)</th>
<th>RLNS n=8 (%)</th>
<th>CD n=31 (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>54 (32-72)</td>
<td>46 (32-59)</td>
<td>55 (32-69)</td>
<td>0.14</td>
</tr>
<tr>
<td>TNM classification after imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0N3M0</td>
<td>2 (5)</td>
<td>0</td>
<td>2 (6.45)</td>
<td>1</td>
</tr>
<tr>
<td>T1N3M0</td>
<td>2 (5)</td>
<td>0</td>
<td>2 (6.45)</td>
<td>1</td>
</tr>
<tr>
<td>T2N3M0</td>
<td>9 (23)</td>
<td>1 (12.5)</td>
<td>8 (25)</td>
<td>0.65</td>
</tr>
<tr>
<td>T3N3M0</td>
<td>11 (28)</td>
<td>5 (62)</td>
<td>6 (19)</td>
<td>0.027</td>
</tr>
<tr>
<td>T4N3M0</td>
<td>15 (38)</td>
<td>2 (25)</td>
<td>13 (41)</td>
<td>0.44</td>
</tr>
<tr>
<td>Cytological evidence of N3-disease before NAC</td>
<td>18 (46)</td>
<td>5 (62)</td>
<td>13 (41)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Histological subtype

<table>
<thead>
<tr>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richardson Grade</td>
</tr>
<tr>
<td>Grade1</td>
</tr>
<tr>
<td>Grade2</td>
</tr>
<tr>
<td>Grade3</td>
</tr>
<tr>
<td>Unknown</td>
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Tumor phenotype

<table>
<thead>
<tr>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple negative</td>
</tr>
<tr>
<td>HR+/HER2-</td>
</tr>
<tr>
<td>HER2+</td>
</tr>
</tbody>
</table>

RLNS group: radical lymph node dissection; CD group: conventional lymph node dissection; NAC, neoadjuvant chemotherapy; HR, hormonal receptor; HER2, human epidermal growth factor receptor 2.

18FDG-PET/CT imaging acquisition and interpretation. Patients fasted 6 h and blood glucose level had to be less than 7 mmol/l. 18FDG (5 MBq/kg) was injected in the arm opposite to the tumor. Imaging was performed 60 min later, from mid-thigh level to the base of the skull, with the arms raised, on a Gemini XL PET/CT (germanium oxyorthosilicate-based PET+16-slice CT; Philips Medical system). CT data were acquired without contrast-enhancement and using the following parameters: 120 kV; 100 mAs; pitch 0.94; slice thickness 2.5 mm. PET data were collected in a 3-dimensional mode, with 2 min per-table-position, and reconstructed. PET/CT interpretation was performed by two nuclear medicine specialists who had no knowledge of the results of conventional imaging. If the interpretation differed, consensus was reached with the help of a third reader. Lymph node evaluation and interpretation of distant foci were performed as previously described (4, 6). 18FDG uptake and CT findings were considered altogether (4, 6).

Histology. The histological subtype was confirmed by performing a biopsy before primary chemotherapy. Estrogen and progesterone receptors were considered positive when receptor expression attained at least 10%. The Scarff-Bloom-Richardson classification was used for tumor grading. The tumor was defined as triple negative in the absence of estrogen or progesterone receptor expression and when it did not over-express human epidermal growth factor receptor 2 (HER2). Patients with strong immunohistochemical (IHC) positivity for HER2 (3+) and patients with HER2-positive tumors by fluorescence in situ hybridization (FISH) were considered as having a positive HER2 status.
Clinical staging was according to the TNM classification and the staging system was according to the American Joint Committee on Cancer (AJCC) classification (2).

Statistical analysis. Data were analyzed using the Fisher’s exact tests, $\chi^2$ test and Student’s t-test. Overall survival (OS) and disease-free survival (DFS) were calculated by the Kaplan-Meier method and measured starting on the date of surgery. The log rank test was used for the univariate comparison of survival endpoints. A $p$-value of less than 0.05 was considered statistically significant. Analyses were performed using the R 2.15.3 statistical software (www.r-project.org).

Results

Patients’ and tumor characteristics. Thirty nine patients fulfilled the inclusion criteria. The main patients’ and tumor characteristics are listed in Table I. The median patient age was 54 years (range=32-79 years). Fifty-nine percent of patients were post-menopausal at the time of diagnosis. Only 14 patients (36%) were classified as having N3 disease at the physical examination. Forty-six percent of patients had cytological evidence of N3 stage disease before NAC. Fifty-four percent of the patients had a tumor size exceeding 5 cm or inflammatory breast cancer. PET/CT was performed at the time of the initial assessment in 95% of cases and it helped change the disease stage in 64% of the patients ($n=25$). Stage IIIC was revealed in most cases by PET/CT ($n=23$) or by conventional imaging ($n=2$).

The most frequently encountered histological subtype (according to the WHO classification) was invasive ductal carcinoma (87%). Hormone receptors were positive on the initial biopsy in 20 patients (51%). The HER2 receptor detected by immunohistochemistry or FISH was positive in 10 patients (25%). Thirteen patients (33%) had a triple-negative tumor. N3 disease was more frequent in patients with grade 3 tumors (61%).

Treatment and pathological findings. Thirty-six patients (92%) had received NAC. Out of these patients, thirty-three (91%) had received anthracycline-based chemotherapy, 29 (80%) taxane-based chemotherapy and 3 (8%) combination treatment of capecitabine-vinorelbine. Chemotherapy regimens differed between the two centers.

Surgery was either mastectomy ($n=30$) or breast-conserving ($n=9$), associated with conventional axillary lymph node dissection ($n=31$, CD group) or radical axillary lymph node dissection ($n=8$, RLNS group). Four patients in the RLNS group had undergone a supra-clavicular lymph node dissection.

In most cases, no additional preoperative imaging had been performed prior to surgery. Most of time, the decision to perform a radical lymph node dissection was made intraoperatively by palpation.

Sixty-four percent of the patients had exhibited persistent nodal involvement after primary chemotherapy (seven patients, all in the RLNS group). A total remission of the breast tumor had been achieved in 23% of the patients. Only 17% of patients had achieved a complete response of both the breast tumor and lymph nodes. The positive supraclavicular node rate was 20% ($8/39$).

The median number of lymph nodes dissected was 10 (range=2-27). In the RLNS group and in the CD group, the median number of positive lymph nodes was statistically different ($11 (2-14)$ and $2 (1-9)$, respectively, $p=0.015$).

Eight patients had received adjuvant chemotherapy. Locoregional radiotherapy had been delivered to 33 patients. The axilla had been irradiated in 12 patients (more than half of the axillary nodes were positive in 7 and 5 had more than
4N+). After radiotherapy, trastuzumab had been administered systematically to patients with HER2-positive tumors (n=10). Twenty patients had received hormonal therapy, either tamoxifen (n=7) or an aromatase inhibitor (n=13).

Morbidity, recurrence and survival. The median follow-up period was 24 months (range=1-59). It was 15 months (1 to 30.5) in the RLNS group and 25 months (1 to 59) in the CD group.

Short- and long-term morbidities were limited in our patients. In the RLND group, only two patients had experienced hyperesthesia of the arm, while minor lymphedema had occurred in one patient. No major lymphedema had been reported; however, patients had not been systematically evaluated.

The overall recurrence rate was 23% (9/39). Distant metastases occurred in 8 patients with involvement of lung (n=3), mediastinum (n=3), liver (n=3), bone (n=2), brain (n=2) and contralateral axillary nodes (n=1). Five patients developed a locoregional recurrence: chest wall (n=3), homolateral axilla (n=3) and supraclavicular area (n=2). Patients with locoregional recurrence also experienced a distant relapse. Five patients with a recurrence died during follow-up.
Among the 8 patients who had undergone RLNS, three relapsed. Two patients developed distant metastases and only one developed an isolated local recurrence (into the chest wall).

The median time to recurrence was 20 (1.7-24) and 18 months (1.5-37) in the RLNS and CD group, respectively. There was no statistically significant difference between the two groups.

The 2- and 5-year overall survival rates of all patients were 90% and 65%, respectively.

The 2-year overall survival rate in the RLNS group was 100%, whereas it was 82% in the CD group ($p=0.25$) (Figures 1 and 2).

Discussion

Since a long time, the management of patients with locally advanced breast cancer was a subject of controversy until the era of multimodality therapy. With the modification of the AJCC staging system in 2002 in order to treat patients with N3 supraclavicular disease alone with a curative multimodal approach, studies have confirmed that patients with supraclavicular metastasis at diagnosis have significantly better outcomes than patients with distant M1 disease (2, 5, 7). Olivotto et al. observed an overall survival rate of 13.2% at 20 years for nodal-M1 cases and 1.3% for (other) M1 cases ($p<0.0005$) (7). In the era of $^{18}$FDG-PET/CT, the number of patients diagnosed with ipsilateral supraclavicular lymph node involvement (stage IIIC) on imaging and no clinical symptoms is increasing (6). The use of imaging has become increasingly common for staging in advanced breast cancer. In our study, most of the potentially involved lymph nodes, namely ipsilateral axillary, infra-clavicular, internal mammary and supraclavicular nodes, were identified by PET/CT or conventional imaging. $^{18}$FDG-PET/CT leads to a disease stage modification in 25 out of 37 patients (68%). However, findings were confirmed by cytology or biopsy in only 43% of patients.

Extensive lymph node surgery in case of N3 disease has not yet been well-evaluated in the era of multimodal treatment and $^{18}$FDG-PET/CT staging. To our knowledge, our series is the first to study the impact of RLNS in patients with N3 breast cancer without metastatic disease in the context of multimodal therapy. We herein reported data concerning 39 patients with advanced breast cancer classified as having N3 disease. Eight out of these patients had undergone RLNS, while the others had undergone conventional surgery. No statistical difference was evidenced in the prognosis or locoregional control between the two groups. On the opposite, an impact has been observed by Chen et al. in a recurrence setting (8). However, our study has certain limitations. Its retrospective nature could have generated some bias. The type of lymph node dissection was not the only difference between the patients. Treatment was not uniform; especially the chemotherapy regimen and targeted therapy were different between the beginning and the end of the study and between the two Centers.

The decision to extend surgery should be based on the risk of residual lymph node disease, the impact of this residual disease on patient outcome and the risk of surgical morbidity. Assessing response to lymph node disease can be difficult. Combined with magnetic resonance imaging (MRI), PET/CT can help detect the location of residual disease, as clinical exploration during surgery can be limited. We propose a pilot multi-Center study including $^{18}$FDG-PET/CT and MRI during NAC in order to guide the extension of post-NAC surgery (Figure 3). PET/CT is helpful to detect N3 disease at initial staging (4, 6); however, the use of PET/CT to predict breast residual disease after NAC is debated. It has been suggested that $^{18}$FDG-PET could be used to assess the pathological response in the primary breast cancer after the completion of the neoadjuvant chemotherapy (9, 10). The reduction rate of $^{18}$FDG uptake between the baseline examination and the PET performed after the end of NAC was only partially predictive of pathological response (9, 10). These results were not found by other teams (11, 12).

If PET/CT after the completion of NAC suffers limitations to predict pathological responses, many studies showed that the variation of $^{18}$FDG uptake between baseline PET and PET performed after two courses could predict pathological response in the primary breast carcinoma (13-15).

Confirming a pathological complete remission (pCR) in axillary lymph nodes, which can modify further treatment, is a strong prognostic factor (16). Indeed, RLNS could help confirm the prognosis but the therapeutic impact of this procedure remains uncertain.

In conclusion, we did not demonstrate a positive impact of RLNS on survival for breast cancer patients with isolated N3 disease but surgical management, although performed in two expert centers, was often heterogeneous. This could be due to the lack of a recommendation for the extension of surgery in such cases. We propose a pilot study to help define surgical management for these patients after NAC.

Conflicts of Interest

The Authors have no conflicts of interest and no financial disclosure to declare.

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References


1733


