

The Optimal Treatment of the Axilla (Surgery or Radiotherapy) after Positive Sentinel Lymph Node Biopsy in Early Invasive Breast Cancer (OTOASOR trial)

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Axillary lymph node involvement is the strongest independent prognostic factor of breast cancer that also can help the selection of patients for adjuvant systemic therapy. Axillary lymph node dissection (ALND) has long been the standard procedure for staging and treating the axilla in breast cancer patients. ALND provides sensitive staging, effective regional control, but the survival benefit of the procedure has not been unanimously proved. On the other hand however ALND causes substantial short and long term postoperative morbidities (seroma, haematoma, lymphedema, recurrent lymphangitis, numbness, paresthesias, shoulder stiffness and the very rare Stewart-Treves syndrome) which affect adversely the quality of life of these patients.

The sentinel node is the first lymph node to receive lymphatic drainage from the primary breast cancer and, therefore, it is the node most likely to contain metastatic tumor cells. Sentinel lymph node biopsy (SLNB) is becoming the standard for staging the axilla in breast cancer patients in many institutions. SLNB is a minimally invasive surgical technique for staging the axilla in clinically node negative breast cancer patients. SLNB is an equivalent (or possibly more sensitive) staging procedure to ALND with minimal morbidity. Many studies support the concept that SLNB is an acceptable alternative to ALND in patients with clinical node-negative early stage breast cancer with tumors smaller than 3cm. Since March 2000 sentinel lymph node biopsy without routine axillary dissection has become a standard method for the axillary staging of breast cancer in our National Institute of Oncology. The current standard care with positive sentinel lymph node is to make completion level 3 axillary lymph node dissections. However, short-term and long-term side-effects of axillary dissection have always been a concern. An acceptable less invasive alternative for ALND in the case of positive SLNB could be regional nodal irradiation (RNI) covering the axillary tail. In a series of randomized clinical trials no difference was found between ALND and axillary radiation therapy in regional control, survival, and long-term morbidity for early-stage breast cancer.

The optimal treatment of the axilla for patients with cN0 and SLN(+) is controversial. It is not clear, if all patients with SLN(+) need cALND or can the axilla be controlled with axillary radiotherapy after positive SLNB instead of further completion axillary surgical procedure. Irradiation of axillary lymph nodes is highly effective in controlling microscopic disease with equal efficacy and less morbidity than surgical procedures. The Hungarian National Institute of Oncology (NIO), Budapest designed the OTOASOR (Optimal Treatment of the Axilla – Surgery or Radiotherapy) single centre randomized controlled clinical trial to compare cALND to RNI in patients with sentinel lymph node-positive (SLN+) primary invasive breast cancer. The main objective of the trial was to prove equivalent survival and locoregional control for patients with axillary lymph node metastasis by SLNB with reduced morbidity if treated with RNI instead of cALND. Other implications to avoid cALND in these patients are that the lack of information on the absolute number of positive lymph nodes may not influence the administration of adjuvant systemic treatments. The results of our study could support further hypothesis that informations obtained by completion ALND after positive SLNB appears to have no major impact on the administration of adjuvant systemic therapy.

Our Surgical Department started a randomized single center study in July 2002. Patients with less than 3cm early invasive breast cancer and clinically negative axillary lymph node were randomized to one of two treatment groups. If the sentinel lymph node came up as positive, then patients in group B received postoperative axillary irradiation without ALND, while those in group A received standard care. The patients included in the trial were women with primary invasive breast tumors clinically less than 3 cm in diameter and no axillary lymphadenopathy. The following were reasons for exclusion: age over 75 years, pregnancy, non-infiltrating carcinoma, and previous excision biopsy of the breast. Furthermore patients with breast tumor over 3 cm or with clinically evident metastatic involvement of the axilla were also excluded. All patients had preoperative triple diagnosis along with routine blood tests with tumor markers.

Breast-conserving surgery or mastectomy was performed in all patients according to our current surgical protocols. If the primary tumor was not palpable, the radio-guided occult lesion localization procedure was performed to detect the tumor. The SLNB procedure was performed using the combined method of patent blue dye and technetium (99Tc) isotope, but in the last 4 years of the trial we used only the isotope method to detect SLN(s). The patent blue stain was used only when the SLN(s) were not visualized on the lymphoscintigrams. During surgery, we used a gamma probe to detect SLN(s). All radioactive and blue-stained SLN(s) were removed together with all lymph nodes that were suspicious for metastatic by palpation. Patients who were assigned to the ALND arm underwent level I-II cALND during the first operation if the imprint cytology was positive for the removed SLN(s). When the SLNs were found to be positive solely by immunohistochemistry or hematoxyline eosin staining, the patients underwent cALND within 4

to 6 weeks. Removal of at least 6 lymph nodes was mandatory. Those patients who were allocated to the RNI arm underwent no further axillary surgical procedure. Extra-axillary SLNs were not removed.

Breast tumor pathologic workup was done according to the routine institutional guidelines (data on tumor type, tumor size, excision margins, histologic and nuclear grade, estrogen receptor, progesterone receptor, and human epidermal growth factor receptor type 2 status with immunohistochemistry or fluorescence in situ hybridization were given). During SLNB, intraoperative imprint cytology was performed routinely for patients randomized to the ALND arm.. The SLNs were finally processed for histology by serial sectioning (0.5 mm levels) and hematoxylin and eosin (HE) staining but no immunohistochemistry.

After breast-conserving surgery, patients underwent postoperative radiotherapy to the remaining breast tissue and the tumor bed according to the standard institutional radiotherapy protocols. Patients with SLN₊ allocated to the RNI arm were irradiated within 8 weeks after surgery. All 3 levels of the axilla and the supraclavicular fossa were considered target volume. The dose of RNI was 50 Gy in 25 fractions of 2 Gy, 5 days per week. According to our institutional protocol, postoperative RNI in patients undergoing ALND was given to all patients with 4 or more positive nodes (pN2a-3a) and to patients with 1 to 3 positive nodes (pN1a) having other high-risk patient and tumor characteristics. Adjuvant systemic therapies were administered according to our institutional protocols.

Between August 2002 and June 2009, 474 SLN+ patients were randomized to completions ALND (arm A-standard treatment, 244 patients) or RNI (arm B-investigational treatment, 230 patients). Overall, 2,106 patients were randomized for completion ALND (1,054 patients) or RNI (1,052 patients). SLN was not identified in 33 patients (1.6%), 15 patients (1.4%) on arm A, and 18 patients (1.7%) on arm B, these patients were excluded and had ALND. SLN was identified in 2,073 patients (98.4%), 1,039 patients on arm A and 1,034 patients on arm B. SLN was positive in 526 patients (25.4%). Overall, 52 SLN-positive patients were excluded from the study because of protocol violation or patient's preference (17 from arm A and 35 from arm B). At the end of our study 474 patients with positive sentinel lymph node received axillary lymph node dissection (244 patients on Arm A) or axillary radiotherapy (230 patients on Arm B) according their random assignment. In the investigational arm of the trial patients received 50 Gy RNI postoperatively without completion ALND. Therefore, we had information only about the SLN(s), but the pathological status of the non-sentinel lymph nodes remained unknown.

Mean length of follow-up was 70 months (39-116 months) on arm A and 68.6 months (38-115) on arm B (p=NS). At a median follow-up of 5.8 years (last follow-up, May 15, 2012), there were 57 deaths (ALND group, 37; RNI group, 20). The number of patients who died in breast cancer was 23 (9.4%) in the ALND arm, and 14 (6.0%) in the RNI arm. The 5-year rates of axillary recurrence were 1.6% (4 patients) in the ALND group and 1.7% (4 patients) in the RNI group. The 5-year overall survival rates were 84.8% in the cALND group and 91.2% in the RNI group. The Kaplan-Meier survival curves shows overall survival time was very good in both treatment arms, well over 75% percent survived up to the latest follow-up point of the study in both treatment arm. The log rank test shows that there was no evidence (p-value=0.257) of a difference in survival between the two groups. The overall survival rates was substantially greater than the 80-85% anticipated at protocol design. At a median follow-up of 5.8 years, we noted no difference between the completion axillary dissection and regional nodal irradiation groups for the primary endpoint of overall survival. Most patients (81%) in our study had tumors smaller than 3 cm, received breast conserving surgery (83%), and had adjuvant systemic therapy (96%), and thus our results are most directly applicable to these patient subpopulations. Disease-free survival did not differ between the two groups either. Furthermore, the rate of disease recurrence was reassuringly low in the undissected axilla(between1-2%), which was not unexpected in view of similar findings in other studies. In our study significantly more patients received adjuvant chemotherapy in the ALND arm compared to the RNI arm. However, this difference in the administration of chemotherapy is mainly explained by the higher proportion of premenopausal patients and larger tumors in the ALND arm. Therefore, the results of our study support the hypothesis that informations obtained by completion ALND after positive SLNB appears to have no major impact on the administration of adjuvant systemic therapy and can be omitted to avoid inevitable side-effects of cALND.

Clinical Practice Points: The optimal treatment of the axilla for patients with cN0 and SLN(+) is controversial. It is not clear whether all patients with SLN(+) require cALND or the axilla can be controlled with axillary radiotherapy after SLNB+ instead of further completion axillary surgical procedure. Irradiation of axillary lymph nodes is highly effective in controlling microscopic disease with equal efficacy and less morbidity than surgical procedures. Other implications to avoid cALND in these patients is that the lack of information on the absolute number of positive lymph nodes may not influence the administration of adjuvant systemic treatments. The results of our study support the hypothesis that information obtained by cALND after SLNB+ seems to have no major impact on the administration of adjuvant systemic therapy.