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Expert Discussion

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Lymph Node Staging in Invasive Breast Cancer

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Axillary surgery has recently been hotly debated due to newly published data. Prospective trials (ACOSOG Z0011, AMAROS, SENTINA, ALLIANCE) as well as consensus meetings have been published, covering all topics in axillary surgery. However, breast centers all over the world have different treatment modalities regarding axillary staging due to lack of consistent and clear prospective data.

Thus, there are still many open questions: what is the role of sentinel node biospy (SNB) in the neoadjuvant situation? Can we omit axillary surgery (ALND) in sentinel node positive disease or even in all patients? What is the role of axillary field level I and II radiotherapy in case of omitting ALND and sentinel metastasis?

In this expert discussion opinion leaders in the treatment of breast cancer voice their view on state-of-the-art treatment of the axilla. Their differences in interpreting available data for clinical praxis reflect the different treatment procedures in their respective countries. However, there seems to be a common denominator for some of the questions.

Florian Fitzal, Linz

Question 1: What Is the Optimal Method for Axillary Staging in the Neoadjuvant Setting?

Galimberti: Neoadjuvant chemotherapy (NACT) has been shown to sterilize involved axillary lymph nodes in a considerable proportion (approximately 30–40%) of patients. Several studies have demonstrated that sentinel node biopsy (SNB) is feasible and accurate in this setting. Thus, for patients with documented positive axillary nodes (positive fine-needle aspiration, FNA) or for those with a high likelihood of axillary nodal involvement (clinically palpable nodes), NACT and SNB could potentially spare the patient axillary lymph node dissection (ALND). In such cases SNB should be performed after the neoadjuvant treatment because in around 30% of cases the axilla becomes negative. Post-neoadjuvant PET may also be useful to select patients who should proceed immediately to axillary dissection. In fact, pre- and post-neoadjuvant positron emission tomography (PET) with [^{18}F]-2-fluoro-2-deoxy-D-glucose may be useful. Although PET has low sensitivity, compared with both ALND and SNB, its high positive predictive value (PPV) and high specificity make it valuable for staging patients with more advanced disease and, as noted, for guiding the surgical management of the axilla.

Kühn: Axillary surgery is a diagnostic procedure with the primary goal to provide prognostic information for the planning of treatment decisions. The systemic treatment in patients who undergo neoadjuvant therapy is predefined. In these patients the histopathologic response to therapy is an important prognostic factor with a high potential to tailor future treatment decisions. Therefore it would be more reasonable to perform SNB after NACT in order to provide this important prognostic factor. This, however, is associated with less favorable success rates (detection rate, false negative rate) compared to SNB in primary surgery (as shown in the SENTINA trial). This relates especially to patients who initially present with positive lymph nodes and convert to a negative axillary status after NACT. For patients with initially negative lymph nodes the success rates for SNB after NACT appear more favorable although evidence from sufficiently powered prospective trials is lacking. Furthermore, no data regarding oncologic endpoints are yet available for the SLN procedure after NACT.

In summary I can conclude that SNB prior to NACT is a safe procedure that can spare many patients with advanced tumors from axillary dissection. SNB after NACT is an important future perspective that should, however, be performed within clinical trials to provide the urgently awaited data on clinical outcome.

Rutgers: Here, I would like to explain two different situations: the developments in our own clinic, and how I feel axillary staging could be performed in general clinical practice.

At the Netherlands Cancer Institute, patients who are candidates for neoadjuvant therapy will have ultrasound examination of the axilla as well as PET/CT. FNA cytology is

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performed in cases of suspicious lymph nodes. If axillary lymph nodes are proven to be metastatic, an I-125 seed is placed under ultrasound guidance in the largest metastatic node (as well as in the primary cancer). During surgery, after NACT, the marked node (the MARI node, Mapping of the Axilla with Radioactive Iodine seed) can easily be removed with gamma probe guidance. Frozen section is performed: if no cancer is found, no further surgery of the axilla is performed. If the MARI node contains cancer after chemotherapy, an axillary lymph node dissection is performed in the same session. With this strategy, we expect to minimize overtreatment and undertreatment of the axilla in the neoadjuvant setting.

For the 'real-world' situation, I would advise ultrasound examination of the axilla in those patients who are eligible for NACT with FNA cytology or core biopsy of suspicious lymph nodes. We suggest PET/computed tomography (CT) scan instead of the traditional imaging procedures for staging distant disease. In case of a *proven* positive pre-chemotherapy axillary lymph node metastasis, I would perform an axillary lymph node dissection after chemotherapy, since the reliability of postchemo sentinel node biopsy in prechemo-positive patients is questionable. In case of an ultrasound-negative and PET/CT-negative axilla, I would perform a postchemo sentinel node biopsy in combination with the local surgery. If this postchemo sentinel node biopsy is negative, a wait-and-see policy regarding the axilla can be adopted. If it is positive, depending on the estimated tumor load in the axilla, an axillary clearance or radiotherapy of the axilla together with the breast will lead to excellent regional control.

Untch: Basically, there are two scenarios for axillary staging in the neoadjuvant setting: (i) if patients have no suspicious lymph nodes by palpation and ultrasonography in the ipsilateral axilla, the port implant and a sentinel node biopsy can be performed at the same time under general anesthesia. In most cases sentinel lymph node is uninvolved and, therefore, ALND can be spared in the majority of patients after completion of neoadjuvant therapy. (ii) In patients with suspicious lymph nodes (by palpation or ultrasonography) FNA or a tru cut biopsy can be performed. If this reveals macrometastatic involvement in the histology, at final surgery after NACT axillary lymph node dissection would still have to be performed. If patients have a very good clinical and imaging response in the breast and in the axilla and a breast conserving therapy is planned, a sentinel node procedure after neoadjuvant treatment can be discussed with the patient. If 3 lymph nodes (a sentinel and two non-sentinel) are free of tumor cells, the risk of false negativity (uninvolved sentinel nodes but involved lymph nodes in the rest of axillary nodes) is less than 10% according to the ACOSOG study and other data. In this scenario after individual discussion with the patient the decision can be made not to perform ALND. If one or more sentinel nodes are involved after neoadjuvant treatment or a mastectomy is planned, ALND still has to be performed.

For the first scenario we have data from the SENTINA study published in Lancet Oncology 2013. In all patients who have a positive sentinel lymph node before NACT we still have to perform an axillary lymph node dissection after neoadjuvant therapy. Some new data have been presented at ASCO 2014 in Chicago from the SENTINA study in which we try to apply a new model of nomogram calculation. This is important since the probability of axillary lymph node involvement in patients with a pathologic complete remission in the breast is very low. With modern neoadjuvant therapies we can achieve pathologic complete remissions of about 50–70% in selected patient groups (especially with chemotherapy and targeted therapy in patients with HER2-overexpressing tumors or in patients with triple-negative tumors with the addition of anthracycline, taxanes and platinum). It is obvious that we have to also avoid axillary lymph node dissection in these patients.

Question 2: Is There a Subgroup of Patients with 1 or 2 Sentinel Lymph Node Macrometastases Who Do Not Need Axillary Level I and II Clearance?

Galimberti: Several trials (IBCSG 23-01, ASCOG Z0011, EORTC AMAROS) have addressed the question as to whether AD is always necessary if the sentinel node is positive. Only the AZ0011 specifically addressed the issue of the need for axillary clearance in patients with a macrometastatic sentinel node. After a median follow-up of 6.3 years, this trial found no differences in locoregional recurrence, regional recurrence, overall survival (OS) or disease free survival (DFS) between patients, with a positive sentinel node, who received ALND vs. no further axillary treatment. Furthermore, the rate of axillary recurrence was low (0.9% vs. 0.05% in the AD group) even though 27% of patients in the AD group had additional positive nodes. These data suggest it is reasonable and safe to not perform ALND in the presence of 2 macrometastatic sentinel nodes in patients scheduled for breast-conserving surgery (not mastectomy), provided they receive whole breast irradiation and systemic adjuvant treatment.

Kühn: Numerous trials indicate that axillary dissection has little impact on DFS and OS in breast cancer. An important precondition is, however, that adequate multimodal treatment is performed. In fact, most patients with T1/2 tumors and 1 or 2 positive sentinel lymph nodes who undergo breast conserving therapy and tangential field irradiation will not derive any benefit from axillary clearing. It is, however, unclear, if definitely all patients who fulfill these criteria can safely be spared from axillary dissection. So far, no selection criteria are available to define patients with an increased risk, who require axillary surgery. Recent studies (MA 20, EORTC

22922/10925) have shown that regional treatment is associated with improved distant DFS. The reduction of lymph node treatment (including surgery) requires therefore unequivocal clinical evidence. For patients who undergo mastectomy (especially, if no irradiation of the thoracic wall is performed) and patients who undergo partial breast irradiation ALND should still be considered as a standard of care in case of a positive sentinel lymph node.

Rutgers: In our institute, we are inclined to follow the AMAROS trial results in this situation, extending the tangential field a little bit to levels I and II of the axilla. Of course only when radiotherapy of the breast or chest wall is indicated. Further patients should be treated with adequate adjuvant systemic treatments. We have shifted away from irradiation of the periclavicular fields as it has been given in the framework of the AMAROS trial. In patients with limited sentinel lymph node involvement (only 1 lymph node with macro or micro metastatic disease) no further treatment of the axilla is performed in our institute.

Untch: All patients who receive BCS and will receive adequate postoperative tangential field radiotherapy and systemic treatment according to tumor biology and have 1 or 2 involved sentinel nodes can be spared ALND according to the data from ACOSOG Z0011 trial. There are no subgroups of patients for whom this rule should not apply. Patients with mastectomy were not included in this trial and therefore in these patients axillary lymph node dissection is still the standard of care. The alternative of radiotherapy to the regional lymph nodes instead of axillary dissection is not an option as long as data from the subgroup of about 18% patients from AMAROS trial is not published, in which radiotherapy was an alternative to ALND.

Question 3: Is There a Subgroup of Patients Who Do Not Need Any Kind of Axillary Staging?

Galimberti: If by staging is meant SLNB, then in my opinion there are some patients with early breast cancer, who can avoid this staging provided the axilla is clinically negative, and careful ultrasound of the axilla is unequivocally negative. Note however, that this policy is being tested in the ongoing multicentric SOUND (Sentinel Node vs. Observation after axillary Ultrasound) and INSEMA trials, in which cN0/iN0 patients are randomized to no surgical treatment to the axilla vs. SLNB. Probably these prospective trials will answer the question if surgical staging is still necessary.

Kühn: Axillary staging is a diagnostic procedure to determine adjuvant treatment decisions. For many patients (luminal A, HER 2-positive, triple-negative) the systemic treatment is already predefined by tumor biology. In these patients the axillary status tailors only the regional therapy. In women with a very low risk for axillary involvement and who would be candidates for omission of axillary dissection in case of a positive sentinel node the clinical benefit of axillary staging appears questionable. The same relates to the elderly patient with a luminal B tumor, who would be neither a candidate for chemotherapy nor for axillary dissection or regional radiotherapy in case of a positive sentinel lymph node. With the declining role of axillary treatment even in node-positive women the clinical benefit of axillary staging will be increasingly questioned in the future. The German INSEMA study investigates the option of omitting axillary staging in early breast cancer. Any axillary surgery is contraindicated in patients with primary metastatic disease.

Rutgers: Currently, I feel it would be very difficult to identify any subgroup of patients who might not need axillary staging. So far, only very limited retrospective studies have hinted at the existence of any such subgroup. Of course, women over 60 years of age with a screen-detected breast cancer of < 1 cm in diameter in general have a < 10% risk of axillary – microscopic – lymph node involvement. To this end we urgently need further studies to better identify such very low-risk patients on the basis of the biology of their primary breast cancer. A couple of studies are underway where patients with ultrasound-negative axillae and early breast cancer are randomized between a wait-and-see policy and a sentinel node procedure (Milan Institute, the Dutch BOOG study). For current practice, I am liberal in performing a sentinel node biopsy in any patient with proven invasive breast cancer.

Untch: In patients with ductal carcinoma in situ there is no need for axillary staging. In patients with an unsuspicious axillary status by palpation and sonography, with small hormone receptor positive tumors with G1, G2, Ki-67 less than 15% with low proteases (UPA, PAI 1) or low risk by multigene assays, aged over 65, the probability of axillary involvement is extremely low and also there is no consequence from axillary staging for adjuvant chemotherapy decisions. Therefore these patients are candidates for no further axillary staging. Further definitions will be given by a German study (INSEMA), which will start soon and basically will aim to avoid axillary staging in most patients.

Question 4: Please Define the Role of Radiotherapy in Patients either (A) Not Undergoing Any Kind of Axillary Staging or (B) Omitting Level I and II Dissection in Sentinel Lymph Node-Positive Disease (Macrometastasis).

Galimberti: Several studies have shown that axillary levels I and II receive substantial incidental radiation with various breast irradiation techniques. And patients who undergo

breast conserving surgery but no breast radiotherapy have more frequent axillary recurrences (as well as more local recurrences). The role of breast radiotherapy in controlling axillary disease in patients not undergoing sentinel node biopsy or axillary dissection can be inferred from the results of the recently published Italian single-center randomized trial (INT09/98) compared axillary dissection (AD) with no surgical treatment to the axilla in early breast cancer patients with a clinically negative axilla who underwent breast-conserving surgery and residual breast irradiation. After > 10 years there was no difference in DFS or OS between the 2 arms although 9% of the no AD arm had axillary recurrence. These data indicate that whole breast irradiation contributes to limiting axillary recurrence. As regards RT in patients with sentinel node-positive disease this was again addressed by the Z0011 phase III trial. All patients received whole breast radiotherapy as well as systemic adjuvant treatment suggesting that RT is an essential part of treatment when AD is not performed in patients with a positive sentinel node. Radiotherapy directed to the axilla level I/II is not indicated in any case.

Kühn: Axillary dissection and radiotherapy are both associated with excellent regional control rates in clinically node-negative patients with a positive sentinel lymph node, as has been shown in the AMAROS trial. Patients who received radiotherapy had significantly less arm morbidity compared to patients who underwent axillary dissection. However, some questions remain regarding this study, such as the necessity of internal and supra-infra node irradiation. However, I believe that in the future we will have two options for clinically node-negative patients with a positive sentinel lymph node: (i) omission of any axillary treatment and (ii) regional radiotherapy. Patients with a positive sentinel node who undergo mastectomy without radiation of the thoracic wall are the best candidates for radiotherapy. Regional therapy should be based on information from axillary staging. I do not see a role of regional radiotherapy without axillary staging, except for the rare case of a high-risk patient with a detection failure for SLNB. Axillary dissection will in the future be restricted to clinically positive, CNB/FNA proven axillary involvement.

Rutgers: To me, in situation (A) there is no indication for radiotherapy. If, due to the clinical circumstances, the axilla is considered at very low risk of containing lymph node metastases, there is no reason for radiotherapy either. As stated in my answer to question 3, I am of the opinion that we should do axillary staging in every patient with invasive cancer. I would be very reluctant to do 'blind' radiotherapy to the axilla in a very low-risk patient. In the clinical situation as stated in (B), I would advise the following: in patients who have had breast conservation surgery and have an indication for whole-breast irradiation and in post-mastectomy patients who have an indication for chest wall irradiation, we advise radiotherapy to the axillary field (levels I and II) if macrometastatic disease is found in the sentinel node.

Untch: There is no role for radiotherapy in (A) patients not undergoing any kind of axillary staging. Axillary surgery is basically a diagnostic procedure, axillary irradiation is a therapeutic procedure. If there is a need of axillary staging (which should be mainly driven by biologic properties of the primary tumor) there is obviously no role for radiotherapy in this situation. If there is a sentinel lymph node positivity with macrometatases at primary surgery, no ALND has to be performed, according to the ACOSOG Z0011 study, if these patients are going to receive breast conserving surgery and tangential field irradiation. In case of sentinel lymph node involvement and a planned mastectomy the method of axillary staging is ALND. If the AMAROS study is going to publish results on the 18% patients who had a mastectomy to replace axillary lymph node dissection by radiotherapy, this question might be answered in a different way: instead of doing axillary lymph node dissection we could perform an extension of the radiotherapy field to regional nodes. As long as we don't have such data there is no place for radiotherapy instead of axillary lymph node dissection.

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