Clinical Aspects of Sentinel Lymph Node Biopsy

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Question 1: Which Lymphography Technique Should Be Performed? Is the Blue Dye Technique Equivalent to the Use of the Scintigraphic Procedure?

Bauerfeind: Preoperative lymphoscintigraphy is warranted, because it is possible to determine the location and the approximate number of the targets (sentinel nodes) preoperatively. This allows the surgical team to correlate the lymphoscintigraphic results with the intraoperative situation and helps to reduce false negative rates, to raise detection rates and to assure quality, objectivity and reproducibility of the procedure. Compared with the use of radioisotopes, the blue-dye technique may provide similar results with respect to the identification of a sentinel node, but gives no information about how many sentinel nodes have to be removed. Blue dye staining alone may produce more surgical morbidity in the axilla due to ‘undirected searching’ for the sentinel node(s), in contrast to a gamma probe guided sentinel node excision. Therefore, the use of blue dye as additional help to radiocolloid lymphatic mapping should be facultative, whereas the lymphographic technique is obligatory.

Galimberti: Sentinel node identification is more reliable when large-size radio labeled colloids are injected in a relatively small injection volume (0.4 ml). Sub-dermal administration appears to be the best way of injection for palpable lesions. The advantage of preoperative breast lymphoscintigraphy with an anterior chest view after radio colloid injection is that it can reveal potential regional drainage sites outside the axilla. In contrast, the blue dye technique provides knowledge of whether a sentinel node will be identified only during the operation. Axillary tissue has to be dissected ‘blindly’ until the blue node is located, which could be several cm from the incision. Also, vital blue dye does not routinely lead to preoperative recognition of alternative drainage patterns.

Reitsamer: The best method is the combination of the blue dye technique and the radioisotope technique with the gamma probe, although good results can be achieved with blue dye only or radioisotope only. With the combined technique it is easier and more reliable to localize the sentinel lymph node. Scintigraphy is not absolutely necessary, but can facilitate the identification of the sentinel node by optimizing the localization of the incision for sentinel node biopsy.

Rutgers: The most informative lymphoscintigraphy technique to ensure adequate lymphatic mapping is injection of the radioisotope tracer in the vicinity of the tumor. This allows visualization of sentinel lymph nodes in the axilla, but also at other sites, such as internal mammary chain, infraclavicular, supraclavicular and intramammary locations. Scanning could be performed after 20 min, 2 h – and if necessary – 4 h. Injection of radioisotope in the skin or parenchyma will result in uptake of sentinel nodes in the axilla in the vast majority of cases. Thus, if the aim of the sentinel node procedure is to omit unnecessary axillary clearances (i.e., if the target of the sentinel node procedure is only the axilla) then injection of the radioisotope tracer periareolarly, in the parenchyma or subcutaneously over the tumor, will lead to sentinel nodes in the axilla. In that situation, lymphoscintigraphy will add little information, and identification by a gamma probe only will suffice in the vast majority of cases. Since better staging of solid cancers always leads to better patient-tailored treatments, I am very much in favor of the lymphatic mapping technique including intra-tumoral injection of radioisotope, careful preoperative lymphoscintigraphy and search and retrieval of all visualized sentinel nodes. This is a more costly and time consuming technique, but finally it will pay off.

In my opinion blue dye is not equivalent to scintigraphy; it will only lead to sentinel nodes in the axilla, since only the axilla

will be explored after injection of the blue dye. Further, identification of blue lymphatics and blue nodes is somewhat more difficult, particularly in obese patients. With blue dye alone and less experienced hands, the identification rate of the sentinel node in the axilla falls below 90%. To me this is not acceptable.

Untch: All studies with the concomitant use of both methods have shown a significant increase in detection rate with combination of radio colloid and blue dye. Blue dye alone is a compromise in those hospitals where a nuclear medicine department is not available. Preoperative scintigraphy allows planning of surgery and gives a good estimation whether there are multiple sentinels or aberrant locations. Intraoperative measurement with a gamma camera allows identification of possible additional sentinel nodes and assessment of residual radioactivity after node removal. The addition of blue dye on the other hand is a good visual tool to detect sentinel nodes. With blue dye alone surgical trauma seems to be greater, although there are no data to prove this.

Question 2: Should Full Axillary Dissection Be Carried out in Patients with Isolated Tumor Cells or Micrometastases in the Sentinel Node?

Bauerfeind: In the normal routine setting immunohistochemistry of sentinel nodes is not recommended. Therefore, the number of diagnosed isolated tumor cells will be very low. From the literature the prognostic value of isolated tumor cells is not yet clear. The reported risk of axillary non-sentinel lymph node metastases after detection of isolated tumor cells in sentinel nodes is very inconsistent. There is no indication for further axillary dissection if sentinel nodes contain isolated tumor cells. However, the diagnosis of micrometastases in the sentinel nodes leads to further positive non-sentinel nodes in 25% of cases. Therefore, further axillary evaluation has a high impact on adjuvant therapeutic regimens. It is necessary to perform axillary dissection in this situation for further identification of local and systemic risk of relapse.

Galimberti: The prognostic value of micrometastatic sentinel nodes is not well defined. As the European Institute of Oncology we participate in the IBCSG trial which compares, in case of micrometastases in the sentinel node, axillary dissection with no further axillary treatment. Patients who do not enter the trial would receive complete axillary dissection. Outside the trial patients with isolated tumor cells do not receive any axillary treatment.

Reitsamer: For patients who harbor isolated tumor cells only in the sentinel lymph node, no further axillary lymph node dissection should be performed. For patients with micrometastases in the sentinel lymph nodes full axillary lymph node dis-

section should be performed, as there is a low risk of further tumor deposits in non-sentinel lymph nodes.

Rutgers: Deposits smaller than 0.2 mm can be considered isolated tumor cells and in the vast majority of patients full axillary clearance is of no clinical value. In patients with micrometastases (tumor cell deposits between 0.2 and 2 mm) in the vast majority of patients axillary clearance will provide extra information and may improve regional control.

Untch: Isolated tumor cells are usually detected in final paraffin histology. Going back in these patients for second surgery would put them on a much too high risk of surgical overtreatment. In the case of a micrometastasis the risk of additional node involvement ranges between 5 and 20%, depending on additional factors like size of the micrometastasis (the cut-off might be set between 0.2 and 1 mm and between 1 and 2 mm), but also hormone receptor status, tumor size etc. (see question 7). Level 1 and 2 axillary surgery (mostly second surgery, because micrometastases most often are detected in final paraffin sections) is advised, with the risk that 80–95% of patients receive surgical overtreatment. On the other hand, one should give individual patients the possibility of a shared decision. That means that, for example, a 60-year-old, hormone receptor positive patient with a tumor size of less than 2 cm might opt for no further surgery in the case of a micrometastasis of less than 1 mm with a reasonable security of not having additional lymph nodes involved.

Question 3: What Is the Role of Extra-Axillary Sentinel Nodes?

Bauerfeind: The radio colloid is routinely applied subdermally/subareolarly. Extra-axillary sentinel node presentation is therefore very rare. As the finding of a negative axilla and positive extra-axillary nodes is rare, the value of removing any locoregional lymph nodes is questionable and surgical complications after removing extra-axillary lymph nodes are possible, the routine removal of lymphoscintigraphically positive extra-axillary lymph nodes is not recommended.

Galimberti: The most important drainage site outside of the axilla is the internal mammary lymph node (IMN) chain. IMNs can be quickly and easily removed via the breast incision with insignificant risk and no increase in postoperative hospitalization. Patients with a positive IMN are upstaged from N0 or N1 to N3, prompting modification of both local (radiotherapy to internal mammary chain) and systemic treatment; without IMN sampling, they would be understaged. Involvement of IMNs is associated with worsened prognosis. Obtaining information on IMN involvement has an important implication: if it is reasonable to remove the axillary nodes when the sentinel node is positive, then it is consistent to irra-

diate the internal mammary chain when an IMN is positive, in the hope of destroying other IMN metastases.

Reitsamer: As the reduction of morbidity is the main goal of sentinel node biopsy, extra-axillary sentinel nodes should not be excised. For ultrastaging of the patients, the role of extra-axillary lymph nodes still has to be established. No data are available concerning the advantage of extra-axillary staging or ultrastaging.

Rutgers: Although it is rare that extra-axillary sentinel nodes are the only positive nodes, and the nodal state has become less and less important for prognostic information, still between 3 and 5% of patients in whom extra-axillary sentinel nodes are pursued after adequate lymphoscintigraphic mapping, will identify a tumorpositive node otherwise not encountered. These findings will have consequences for the target of radiotherapy (i.e. internal mammary chain and infra- or supraclavicular nodes). The value for prognostic information is limited.

Untch: Sentinel node detection gives us the unique opportunity to excise aberrant nodes. This could be in different locations in the axilla or intramammary region and also internal mammary region. Most of the scintigraphical detection of positive internal mammary nodes occurs in the case of intratumoral colloid injection. There is no study to show whether systematic excision of internal mammary lymph nodes (IMN) can give better local and systemic control. Most of us probably would have strong concerns to use IMN dissection in clinical routine. Some argue that this is a minimally invasive approach to the Halstedian paradigm, which we abandoned many decades ago.

Question 4: Is Sentinel Lymph Node Biopsy a Reliable Method in Patients with Multicentric Carcinoma?

Bauerfeind: As long as the radio colloid is injected in the subdermis of any breast quarter or in the subareolar region the lymphatic drainage goes into the axillar basin in 98% of cases. This fact makes sentinel lymph node biopsy (SLNB) feasible for multicentric breast cancer. There are several studies that have shown practicability and reliability of SLNB with acceptable false-negative and detection rates in multicentric breast carcinoma. However, the reported numbers are very small and the level of evidence is low. In highly experienced institutions SLNB can be offered to patients with multicentric breast cancer.

Galimberti: Nowadays after several publications regarding SLNB in patients with multicentric carcinoma we are allowed to perform SLNB if we have any doubts, since an equal identification rate to that for unifocal tumors and an acceptable

false negative rate are reported. SLNB is our standard procedure for nodal staging in patients with multicentric breast cancer and a clinically negative axilla.

Reitsamer: SLNB is a reliable method in patients with multicentric carcinoma. For axillary staging the sentinel lymph node can be accurately identified independent of localization or number of tumors in the breast. Identification rates and false negative rates are equivalent in multicentric and unicentric disease.

Rutgers: Yes, if cancers are located in the same part of the breast it is very likely that the lymphatic drainage of that quadrant of the breast will be the same and I consider SLNB reliable in those patients. In real multicentric breast cancer, data are limited. However, in my experience it is possible to perform lymphoscintigraphy of two different tumors in two different locations in one breast. This may lead to the same sentinel nodes, but sometimes also to different sentinel nodes. If the principles of the lymphatic mapping are followed, also in real multicentric cancer SLNB should be reliable.

Untch: The first studies with sentinel nodes were performed in unicentric tumors of less than 2 cm. Later we went on to 3 cm and then to 5 cm. Multicentric carcinoma is per se no contraindication to SLNB, provided it is performed in a quality controlled environment, i.e. with radio colloid scintigraphy and gamma camera detection plus blue dye, with excellent surgical expertise, in a hospital with a nuclear medicine department, pathology etc.

Question 5: What Is the Role of SLNB in Patients Receiving Neoadjuvant Chemotherapy? Should SLNB Be Carried out Before or After Neoadjuvant Chemotherapy?

Bauerfeind: For patients undergoing primary systemic therapy (PST) the data in reference to the reliability of SLNB are assessed as insufficient in international consensus recommendations. Sentinel node identification rates are around 90%, the false negative rate ranges between 0 and 33%. However, about 40% of the patients receiving PST have a negative axillary lymph node status and will be overtreated by classical axillary dissection (ALND). Preexisting data regarding SLNB after PST are not acceptable for the implementation into the routine clinical setting. SLNB before neoadjuvant chemotherapy (NCHT) is comparable to the surgical setting in the adjuvant situation. It can be helpful to stratify patients for neoadjuvant or adjuvant options whereas modern indications for NCHT should not follow only measurable tumor burden (size and number of positive lymph nodes) but rather biological criteria of the tumor. For that reasons it seems to be essential to analyze the role of SLNB in neoadjuvant study concepts in a prospective setting as it is done with the German study

SENTINA (sentinel node excision after neoadjuvant chemotherapy) that specifically addresses the questions at issue.

Galimberti: Axillary status at the end of NCHT may differ from that at the beginning. As many as one-third of patients who undergo complete axillary dissection after NCHT will have negative nodes. If SLNB were performed after NCHT, these women would be spared axillary dissection. Axillary nodes can be converted, i.e. down-staged, from N+ to N–, and this alone is an appropriate reason for SLNB after NCHT. No data suggest that the lymphatic pathways are disrupted after NCHT to render SLNB inaccurate. The identification of sentinel nodes after NCHT can be performed with same success as for newly detected stage I/II cancers and false-negative SLNBs are no more likely after NCHT than before NCHT when performed by experienced surgeons. A recent meta-analysis of SLNB after NCHT by Xing et al. [British J Surg 2006;93:539–546] of 1,273 patients in 21 studies, found a sentinel node identification rate of 90% and a sensitivity of 88%.

Reitsamer: Sentinel lymph node biopsy after NCHT is still controversial. To date no group of patients could be identified in which SLNB after NCHT is a reliable method. For patients with advanced disease, who are candidates for NCHT, SLNB will not be a reliable method for axillary staging. As chemotherapy will become the treatment of choice for patients with small tumors, possibly a group of patients will be identified in the future for which SLNB after NCHT could be applicable.

Rutgers: Since half of the patients with larger breast cancers are node negative, also in those patients SLNB is useful. We prefer to perform SLNB before NCHT in all breast cancers, except real locally advanced breast cancer and mastitis carcinomatosus. So we perform SLNB in tumors up to 5–6 cm before chemotherapy. In those situations we have the same identification rate of over 98% and nodal positivity is around 40–50%. If the sentinel nodes are negative, after chemotherapy no axillary clearance is performed. We feel that the false-negative rate of the sentinel node after NCHT (in pooled data 10–12%) is too large. You will miss a positive node in 1 out of 10 patients. However, if this false-negative risk is communicated to the patient and she accepts this, SLNB could also be performed after NCHT. The differences in sparing unnecessary axillary clearances will not differ substantially between the two options: before chemotherapy or after chemotherapy. In both published series the nodal positivity rate is about 40%.

Untch: In our own studies from Germany, 40–70% of patients do not have axillary involvement after NCHT. Therefore in these patients full axillary surgery would be overtreatment. NSABP has performed the biggest study for SLNB after NCHT compared to full axillary dissection. The detection rate

is about 80% the false-negative rate is about 10%. A more biologic approach would be to use SLNB before NCHT. If SLNB is tumor free, after NCHT axillary dissection could be avoided. If SLNB is positive before NCHT, there are two possibilities: full axillary dissection after NCHT or repeat SLNB after NCHT in cases with good clinical and sonographical remission in the breast. If SLNB is negative patients might be candidates for no further surgery. Patients with clinically or sonographically suspect axilla would not be candidates for SLNB after NCHT.

Question 6: What Is the Role of Tumor Size for Selecting Patients for SLNB?

Bauerfeind: The best evidence, including one randomized trial, for an oncologically safe SLNB exists for T1 tumors. However, several trials have shown a safe feasibility and reliability in bigger breast cancers as well. The overall local recurrence rate after SLNB independently from the tumor size is lower than 1%. Therefore, selecting patients for SLNB is not dependent on tumor size but on carefully performed clinical axillary staging (inflammatory breast cancer is excluded from this argumentation).

Galimberti: SLNB is feasible and accurate even in patients with large breast cancers and clinically negative axilla. Axillary lymph node dissection can be avoided in nearly one third of patients by focused examination of the SLNB. The incidence of axillary metastasis is low for patients with small tumors. It increases progressively with the size of the primary tumor, approaching 80% for T3 tumors. The rates of sentinel node identification, accuracy, and false negatives compare favorably with those reported for studies of SLNB in patients with smaller breast tumors. In patients with large breast tumors, focused pathologic examination of the sentinel node could identify the best candidates for axillary lymph node dissection.

Reitsamer: SLNB should be performed for axillary staging regardless of tumor size in patients suitable for primary surgery, although identification rates may be somewhat lower in larger tumors.

Rutgers: Tumor size in itself should not be a reason for not performing SLNB. However, in T1a breast cancers (<6 mm) the risk of nodal involvement is less than 5%. In those patients SLNB could be omitted. Further, in locally advanced breast cancer and very large tumors (>5–6 cm) I am uncertain about the reliability of SLNB.

Untch: With increasing tumor size the rate of positive axillary nodes increases. If irrespective of tumor size the sentinel node is not involved, patients are candidates for no further axillary

surgery. This procedure is safe up to 5 cm tumor diameter. The only contraindication would be a palpable or sonographically suspect node in the axilla.

Question 7: What Is the Role of Nomograms to Detect Patients with a Positive Sentinel Node Who Do not Require SLNB? Should Nomograms Be Used in Routine Clinical Practice?

Bauerfeind: In about 40% of all cases the sentinel node is the only positive lymph node despite a full axillary clearance. The risk of further non-sentinel metastases is dependent on: the size of the primary tumor, the size of the sentinel metastasis, the number of positive sentinel nodes and lymphovascular invasion of the primary tumor. The risk of no further axillary involvement if none of the above additional risk factors are present is around 25%. This risk inclines to 75% in our own study if there is only one more risk factor present [Bauerfeind et al. *Anticancer Res* 2007;26:1929–1932]. Nomograms that address this risk calculation can help to advise patients with one positive sentinel node on questions of local control. Decisions with regard to systemic therapy can already be made by the finding of one positive (sentinel) lymph node. However, it is not clear whether potentially unremoved axillary tumor burden will lead to a worse prognosis if systemic therapy is going to follow. Nomograms can help to reduce unnecessary axillary dissections for a small number of patients who will receive systemic treatment anyway.

Galimberti: In our multivariate analysis of 4,351 consecutive patients, the prevalence of sentinel node metastases was associated directly with tumor size, multifocality, and the occurrence of peritumoral vascular invasion (PVI; all $p < 0.0001$); further, it was inversely associated with a favorable histotype ($p = 0.0007$) and lack of progesterone receptors ($p = 0.004$). A predictive model based on the features more closely associated with sentinel node status documented that patients with a favorable tumor type 1 cm in size and without PVI ($n = 178$, 4% of the population) had the lowest risk of sentinel node metastases (9.5%) whereas patients with tumors >2 cm and with PVI ($n = 250$, 5.7% of the population) had the highest risk (77.2%) of sentinel node involvement. Tumor size and PVI emerged as the most powerful independent predictors of sentinel node metastases. Although no combination of features identified patients with a $<9.5\%$ risk of sentinel node metastases, the current data may be used to tailor the management of patients with breast cancer with the aim of minimizing the diagnostic and therapeutic procedures as much as possible, thus improving the quality of life of the patients without any adverse effect on their survival rates.

Reitsamer: The use of nomograms for the prediction of involvement of non-sentinel lymph nodes in sentinel node posi-

tive patients is speculative and is based on probability calculation. Some authors found that nomograms did not correlate in different patient populations. Until it can be demonstrated which variables are the best predictors for non-sentinel lymph node metastasis and until there is a standardization for the use of nomograms, they should not be used in routine clinical practice for a decision on full axillary dissection in sentinel node positive patients.

Rutgers: I don't see any help of the nomogram in the clinical situation, since the nomogram cannot exclude the risk of non-sentinel lymph node involvement less than 10% with great reliability. Furthermore, the nomogram does not give adequate information in patients with isolated tumor cells or submicrometastases. The decision to not perform an axillary lymph node dissection after sentinel node procedure with isolated tumor cells should be reached in a multidisciplinary team, taking into account the size and type of the tumor (for instance in larger infiltrating lobular carcinomas in younger patients, I would be more reluctant to omit axillary dissection), together with the pathologist.

Untch: If the sentinel node is positive, the rate of tumor free nodes after complete axillary dissection ranges between 40 and 60%, meaning that these patients receive surgical overtreatment. Nomograms using algorithms including tumor size, grading, receptor status and lymphovascular invasion have shown a good prediction for involvement of further nodes in the case of positive sentinel nodes. Studies should clarify the role of nomograms for further surgery versus no further surgery in the case of positive sentinel nodes. As long as these data are not available there is no other possibility than to perform an axillary dissection if the sentinel node is positive.

Question 8: How Do You Manage Patients with Exclusively One Positive Intramammary Sentinel Node?

Bauerfeind: There are no data regarding this question. There is no experience whether a single positive intramammary lymph node is able to compromise lymphatic drainage to the axilla. If clinical staging of the axilla fulfils all criteria that allow 'normal' SLNB it can be performed despite the positive intramammary finding, presuming the patient's informed consent. Systemic treatment decisions will be already influenced by primary tumor characteristics and the positive intramammary node.

Galimberti: Axillary lymph node status remains one of the most important features for defining the risk category of breast cancer and metastases of the IMNs, which are prognostically considered as axillary nodes, do not show a worse prognosis.

Reitsamer: In patients with exclusively one positive intramammary (sentinel) lymph node, the identification and biopsy of the axillary sentinel lymph node should be performed and the patient should be managed according to the sentinel lymph node status in the axilla.

Rutgers: In general, I would advise this patient to have a axillary lymph node dissection or radiotherapy of the axilla, together with the breast, in case of breast conserving therapy.

Untch: Intramammary sentinel node involvement probably does not have the same predictive role as an involved axillary sentinel node. There are three scenarios: If the axillary sentinel node is tumor free and the intramammary sentinel node is also tumor free, there is no need for further surgery. If the axillary sentinel node is free, but the intramammary node is positive, there is no need for further surgery. If the intramammary node is free but the axillary sentinel node is involved, further dissection is advised.

Question 9: How Do You Manage Patients with an Intramammary Recurrence after Breast Conserving Surgery and SLNB?

Bauerfeind: There are few retrospective case control observations that report an ‘SLNB after SLNB concept’ as feasible and reliable. The reported numbers are very small and the level of evidence is low. Nothing is known about possible neolymphangiogenesis and spontaneous lymph vessel re-anastomosis after lymph node excision. No experience exists whether a negative sentinel node after SLNB is predictive for the rest of the axilla. The risk of a positive node in breast recurrence is probably dependent on tumor characteristics of the primary tumor and the recurrence. The question could only be answered by a clinical trial that performs an axillary clearance independently of the sentinel status. However, it is more than questionable whether such a trial will ever be realized. If preoperative clinical and sonographical staging shows no evidence of a positive lymph node with regard to local control it is acceptable, presuming the patient’s informed consent, to perform SLNB after SLNB as long as any kind of systemic treatment will follow.

Galimberti: Prior axillary surgery is not a contraindication; SLNB appears to work well in the reoperative setting and following previous radiotherapy. In fact, a surgical interruption of lymphatic drainage produces only a temporary blockage; a new lymphatic pathway is soon established. A second SLNB after previous SLNB is technically feasible and likely to prove effective in selected breast cancer patients. These findings are particularly relevant for patients with recurrence in the con-

served breast, whose cancer was previously staged by SLNB. A larger population and longer follow-up are necessary to confirm these preliminary data.

Reitsamer: In most patients with ipsilateral recurrence after breast conserving surgery and SLNB a salvage mastectomy and axillary lymph node dissection should be performed. In rare cases (request of the patient, no radiotherapy after initial surgery) breast conservation for a second time with obligatory radiotherapy and axillary lymph node dissection can be performed. A secondary sentinel lymph node biopsy after a primary sentinel lymph node biopsy is not yet evaluated and is not an adequate management.

Rutgers: I perform lymphatic mapping and lymphoscintigraphy, blue dye and sentinel lymph node procedure again in patients with a relapse one year after initial treatment.

Untch: If the recurrence is ductal carcinoma in situ breast conserving therapy is advisable. If the recurrence is invasive, SLNB can be performed again. If the sentinel is tumor free, there is no strong indication for further axillary surgery.

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