Clinical relevance and refinement of the sentinel node procedure in breast cancer and melanoma
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CHAPTER 12

SUMMARY, CONCLUSIONS AND FUTURE PROSPECTS
The technique of lymphatic mapping in breast cancer is certainly not as standardized as in melanoma. Also, the clinical relevance of extra-axillary sentinel nodes is not yet clear. However, axillary staging by means of the sentinel node procedure with the aid of radioactive tracer, lymphoscintigraphy and blue dye has proven its surplus value over the axillary lymph node dissection. CHAPTER 2 provides a succinct introduction on the procedure in breast cancer.

The intratumoral route of tracer administration has been carefully researched at our institute and makes sense from theoretical and practical point of view. The sentinel node identification rate is 97% with intratrasional tracer administration, which is similar to the results obtained with other routes of administration. It is too early to tell how the sensitivities of the various approaches compare. Long-term follow up of patients with a tumor-free sentinel node and without axillary node dissection will provide us with that information. The intratumoral injection technique with its advantages and disadvantages is discussed in CHAPTER 3.

This injection technique has not been compared with peritumoral or other intraparenchymal injection techniques in a randomized trial so far. CHAPTER 4, however, describes a case in which a patient with a non-palpable lesion received an intraparenchymal tracer injection by accident. Lymphoscintigraphy revealed two sentinel nodes in the axilla. A second dose of Tc-99m-nanocolloid was injected the next day into the primary tumor through a catheter that had been inserted under ultrasound guidance the day before. Once more, a lymphoscintigraphic image was obtained, which showed additional sentinel nodes in two different regions outside the axilla. This observation supports the contention that lymphatic watersheds exist in the breast and stresses the importance of tracer administration into or close to the tumor. This contention is also being backed up by the results presented in CHAPTER 5. Twenty patients scheduled for excisional biopsy of a breast lesion were investigated. Preoperative lymphoscintigraphy visualized at least one sentinel node in all twenty patients. After the excisional biopsy, a discrepancy in the drainage patterns was seen in fourteen out of the twenty patients. Therefore, the reproducibility of the overall lymphoscintigraphic results was 30% (CI: 14 – 53%). A change in drainage pattern to the axilla after excisional biopsy of the breast lesion was seen in nine patients (45%): the original sentinel node could not be visualized in six patients whereas additional hot spots were visualized in the other three. Drainage to the internal mammary chain was preoperatively seen in ten of the twenty patients. The reproducibility of drainage to the internal mammary chain was 20% (CI: 4 – 56%). The location of the hot spot changed to another intercostal space in six patients whereas in two patients, no hot spot was visualized in the internal mammary chain the second time around. Two important conclusions can be made from this study. First, excisional biopsy of the breast causes non-visualizaton of axillary sentinel nodes in more than one third of the cases. Secondly, the locations of the internal mammary chain sentinel nodes visualized after excisional biopsy should not be trusted. This study implies that sentinel node biopsy should be performed prior to excisional biopsy to ensure optimal sensitivity. Therefore, optimal diagnostic procedures other than an excisional biopsy should be performed preoperatively.

The lymphatic drainage patterns from the breast from 700 sentinel node procedures are described in CHAPTER 6. Preoperative lymphoscintigraphy was performed after injection of 99m-Tc-nanocolloid into the tumor. The sentinel node regions suggested by lymphoscintigraphy were verified intraoperatively with the aid of a gamma-ray detection probe and patent blue dye (1.0 ml, into the lesion). Lymphatic drainage to either an axillary or an extra-axillary basin was
observed in 678 patients. Drainage to the axilla from the upper outer quadrant, upper inner quadrant, lower outer quadrant, lower inner quadrant and center was 95.8%, 93.1%, 97.7%, 88.0% and 100% respectively. A sentinel node in the internal mammary chain region was seen in 10.4%, 32.4%, 29.5%, 52.0% and 23.7% respectively. In addition to the axilla and the internal mammary node chain, drainage occurs to other locations in and around the breast in a substantial percentage of the patients (supraclavicular, infraclavicular, interpectoral and intramammary sentinel nodes). Both palpable and non-palpable lesions drain towards the internal mammary chain, although the latter more frequently \( (P=0.001) \), regardless of the quadrant. The lower inner quadrant has less drainage to the axilla compared to the other quadrants, but more to the internal mammary chain. The lateral side of the breast often drains to the internal mammary chain as well (10-30%), but less frequent than medially located tumors \( (P<0.001) \). The observation of difference in drainage from within the breast also supports the contention that lymphatic watersheds exist in the breast.

The latter study showed that drainage to the internal mammary chain is frequent. Whether sentinel nodes in this area should be removed is discussed in CHAPTER 7. Of 691 consecutive patients, a sentinel node was visualized in the internal mammary chain in 150 patients (22%). These nodes could be harvested in 130 patients (87%) without appreciable morbidity and contained metastases in 22 of these 130 cases (17%). In nine patients, the internal mammary chain sentinel node was tumor-positive while the axilla was tumor-free (7%). Stage migration was seen in all patients with a tumor-positive internal mammary chain sentinel node (17%) and led to a better selection of patients who might benefit from postoperative radiotherapy to the internal mammary chain and from adjuvant systemic treatment. Only prospective randomized trials can determine if this will result in improved disease-free and overall survival. It is questionable whether such studies will ever be conducted. Therefore, the decision to begin the hunt for the internal mammary chain sentinel nodes should be based on the established improved staging and common sense.

CHAPTER 8 focuses on defining a false negative sentinel node procedure. The definition is more complicated than it seems and has substantial implications for the false negative rate. Three credible definitions of a false negative finding on sentinel node procedures are given. The first one follows the original definition of the sentinel node, which is based on direct drainage from the primary lesion site and has been used universally in learning phase studies. The second definition is based on the assumption that the results of the procedures are truly positive if a tumor-positive node is found during the standard sentinel node procedure within the limits of its protocol. Finally, one can call the results of a sentinel node procedure false negative only if axillary recurrence occurs during follow-up evaluation. The second definition best serves the clinical purpose, which is to establish metastatic disease but in the least disruptive manner, because it encourages removal of apparently tumor-positive, non-sentinel nodes while discouraging the indiscriminate removal of non-sentinel nodes that is tempting when following the last definition. To enable comparison of false negative rates between different institutes, either consensus should be obtained or a detailed description of the definition used should be given when results of sentinel node procedures are published.

When following the first definition, nine false negative procedures were encountered at The Netherlands Cancer Institute. These cases are discussed in CHAPTER 9. Two false negative results came to light by confirmatory axillary lymph node dissection during the learning phase. Tumor-positive lymph nodes were incidentally found in the axillary tail of the simple
mastectomy specimen in two patients. Excision of a firm, non-radioactive, unstained but tumor-positive non-sentinel node occurred in three other patients. One patient developed an axillary recurrence 22 months postoperatively. Presumptive causes were surgical delay, pathological sampling error and tumor blocking. Therefore, intra-operative palpation of the axilla to identify suspicious lymph nodes is recommended and in a two-day protocol, surgery should be performed first thing in the morning. Seven slices of 50 to 150-µm should strike an acceptable balance between sensitivity and work load for the pathologist.

An evaluation of the results of the sentinel node procedure in 250 melanoma patients with a median follow-up of six years is discussed in Chapter 10. Lymphoscintigraphic visualization was 100% and surgical identification was 99.6%. In 60 patients (24%), one or more sentinel nodes were tumor-positive at initial pathology evaluation and underwent an additional lymph node dissection. Late minor complications after sentinel node biopsy of the remaining 190 patients were seen in 35 patients (18%). The false negative rate was 9%. In-transit metastases in sentinel node negative and sentinel node positive patients were seen in 7% and 23% respectively. The estimated five-year overall survival rates were 89% and 64% respectively \((P<0.001)\). So should the sentinel node procedure be standard in melanoma patients? The main reasons to do so are that the sentinel node status is the strongest independent predictor of outcome in patients with melanoma and that the sentinel node biopsy provides more accurate staging. Furthermore, the procedure can be used to identify patients at high-risk of systemic disease and interested in participation in clinical trials on adjuvant therapy. However, no standard regional or adjuvant systemic therapy with confirmed impact on overall survival has been identified yet. The substantial false negative rates in some studies, the morbidity and the seemingly high incidence of in-transit metastases have to be weighed against the possible survival benefit of early removal of lymph node metastases and the prognostic information. Chapter 11 further discusses the problem of in-transit metastases. In-transit metastases are recurrences which are difficult to treat because they are usually multiple and they tend to recur. The group of patients with a tumor-positive sentinel node undergoing regional lymph node dissection have a higher incidence of this type of recurrence not only when compared to the group of patients with a tumor-free sentinel node, but unfortunately also when compared to those dissected for palpable nodes at a later stage (23.0% vs. 8.3%). Further research on the incidence of in-transit metastases is encouraged.

Conclusions and Future Prospects

Melanoma

The regional lymph nodes are often the initial target for metastasis in melanoma patients. The incidence of blood-borne metastases and the incidence of lymph node metastases are around 20% each.\(^1\) The incidence of occult metastases in the lymph nodes depends on the Breslow thickness and varies from 0% to 60% for various stages. The first recurrence is noticed in the lymph nodes in half of the patients.\(^2\) There is an unresolved debate over the most effective management of the patient whose lymph nodes are presumably negative on clinical assessment.\(^3,4\) Elective (prophylactic) lymph node dissection is not beneficial when the melanoma is thinner than 1 mm, since lymph node metastases are exceptional in these patients. When the lesion is over 4 mm thick, elective lymph node dissection probably makes little sense either, because the prognosis is determined by the distant metastases that are frequently present in such patients. For patients with melanomas
between 1 mm and 4 mm thick, however, the course of action is not clear. The incidence of occult lymph node metastases is relatively high and the incidence of distant metastases is low. It makes sense to assume that there is a survival benefit obtainable by carrying out elective lymph node dissection in these patients. Some large (retrospective, but meticulously analyzed) studies indeed suggest such a survival benefit. One prospective, randomized study did show a survival benefit in some subgroups of patients. However, a survival benefit has not been confirmed by several other prospective randomized trials nor in a meta-analysis.

The ultimate purpose of lymphatic mapping is to provide sentinel node positive patients with early therapeutic measures, like regional node dissection and adjuvant systemic treatment. The only study that examines whether early regional node dissection increases the cure rate has enrolled 2,001 patients and was closed in March, 2002. The final results of the study are not expected before the year 2005. The sentinel node procedure should, until then, be seen as an additional procedure with additional disadvantages such as general anesthesia, prolonged operation time, higher costs and complications. In addition to that, high false negative rates have been reported. The high incidence of in-transit metastases in sentinel node-positive patients is yet another problem. Two questions arise: why are the incidences among different institutes so different? And why is there a higher incidence of in-transit metastases in sentinel node-positive patients in the first place?

MICROMETASTASES

An important question on the minds of surgeons, pathologists and oncologists is the relevance of micrometastases (0.2 mm - 2.0 mm) in sentinel nodes. What should be done with a patient in whose sentinel node contains a few scattered malignant cells? Were these cells simple detached from the primary lesion without the potential to remain viable and divide? Or would these cells have multiplied and become palpable had the sentinel node not been taken? Does their presence mean that the next node in line also contains tumor cells and should be removed? Could these few cells perhaps have been sources for distant metastases and should the patient be treated with adjuvant systemic medication? It seems that medical oncologists in the U.S.A. feel the pressure to do so. A number of current and future trials will answer these questions. A meta-analysis by Dr. Santo Oliveira Filho from Sao Paolo and work from by Dr. Hoon’s group in Los Angeles showed that melanoma patients with histologically tumor-negative but PCR-positive sentinel nodes had a higher recurrence rate than patients with both histologically and PCR-negative sentinel nodes. Dr. Reintgen from Lakeland also found a better overall survival in the latter group.

Unpublished work from The Netherlands Cancer Institute showed additional lymph node involvement of 8 out of the 31 breast cancer patients with a micrometastases in the sentinel node (26%). Seven of these eight patients even had macrometastatic disease in the nonsentinel nodes. In the literature, similar percentages are given. This suggests that treatment of the axilla should be performed if the sentinel nodes contain only a micrometastases. Others showed that the rate of nonsentinel node tumor involvement increased with the size of the primary tumor: if a primary breast tumor is small and if sentinel node involvement is micrometastatic, then tumor cells are unlikely to be found in other axillary lymph nodes.

TECHNIQUE

It is becoming clear that performing a lymphoscintigraphy together with the intra-operative use of a gamma-ray detection probe and blue dye a radioactive tracer are mandatory to identify the
sentinel node. Several studies have shown benefits of the use of these techniques together, as they are complementary.\textsuperscript{17,18} The intra-operative use of a gamma probe, however, can only provide radioactivity counts. Direct visualization of the spatial distribution of radioactivity could facilitate surgery. Several types of hand-held gamma cameras for intra-operative use have been put on the market, but only several phantom and clinical pilot studies with small numbers have yet been published.\textsuperscript{19,21} The field of view ranges from 3x3 cm to 5x5 cm and the acquisition time is between 10 seconds and 3 minutes. At The Netherlands Cancer Institute, we had the privilege to use two different hand-held gamma cameras. The resolution of these cameras seemed slightly bigger when compared to the gamma-ray detection probe. However, the additional value of the hand-held cameras in the sentinel node procedure in breast cancer and melanoma appeared to be scanty. This will be a development to keep an eye on.

There is still a search for new optimal radiopharmaceuticals. Only recently, Dr. Wallace described early clinical results from studies with a new receptor-binding tracer: \textsuperscript{99m}TcDTPA-mannosyl-dextran (Lymphoseek).\textsuperscript{22} Twelve women with breast cancer were randomly assigned to lymphoscintigraphy with either filtered \textsuperscript{99m}Tc-sulfur colloid or Lymphoseek. Lymphoseek exhibited a significantly faster injection site clearance. The sentinel node uptake of both agents varied widely with the same mean. The investigators hope to demonstrate reduced distal nodal uptake in a subsequent study.

Pathologists are also looking for ways to confirm that the correct node was taken. The simplest approach was pioneered by Cochran from Los Angeles and involves charcoal particles to be added to the tracers. These remain in the lymph node and are identified with the microscope. There is a more important advantage: the lymphatic flow from various regions of the body into the sentinel node is compartmentalized. A particular area will drain to only a specific portion of a node. So, the charcoal particles are lodged in the area where tumor cells most likely are to be found and they will focus the pathologist’s attention further. This will most likely increase the amount of micrometastases found in sentinel nodes. Unfortunately, there is still doubt about the clinical relevance of such small metastatic deposits.

\section*{Genomics and Proteomics}

Genetic analysis should enable us soon to determine the biology of the disease based on analysis of the primary lesion.\textsuperscript{23} Meaningful predictions of the course of the disease will be the result and also the tailoring of treatment to the needs of an individual patient. Micro-array analyses will, for instance, tell us that a particular patient may benefit from adjuvant chemotherapy because his or her particular tumor has a tendency for dissemination to distant sites. One study has already shown that this may be possible in breast cancer.\textsuperscript{24} It was concluded that a previously established 70-gene prognosis profile is a more powerful predictor of outcome of disease in young patients with breast cancer than clinical and histologic criteria. If these results are confirmed, the conservative management of breast cancer has been taken yet another step ahead and the need for axillary staging - and sentinel node biopsy - may be less urgent. On the other hand, the biology of the tumor clones that make up a lymph node metastasis may prove to be even more relevant for a patient’s future.\textsuperscript{25} This would emphasize the need for accurate lymph node staging even more.

The use of the micro-array technique may also be beneficial in melanoma. Perhaps patients with a higher risk of in-transit metastases can be selected or even more important: this approach might provide an independent predictor of outcome similar to the sentinel node status. Once again, this could imply that the sentinel node procedure would be unnecessary by then.
Proteomics is another novel diagnostic technique. The main difference between genomics and proteomics is that the genome is a static collection of genes, whereas the proteome is not a concrete entity, but rather a dynamic collection of proteins for the identity, quantity and function. This collection reflects both the intrinsic genetic program of the cells as well the impact of its immediate environment. Proteome studies can therefore complement genome studies, but it remains uncertain whether a protein profile will further improve the prediction of disease progression.

OTHER CANCERS
The sentinel node procedure is gaining ground in other cancers such as urologic, gynecologic and gastrointestinal cancers. A rapidly increasing number of studies is being presented at various large meetings, in particular on gastrointestinal cancers. At the Third International Sentinel Node Congress in 2002, the number of presentations on this tumor type was 75, up from two at the Second International Sentinel Node Congress in 1999. The standard treatment for early gastric cancer in Japan is gastrectomy with an extensive en bloc lymph node dissection. The appeal of lymphatic mapping is that just a limited excision of the part of the stomach containing the tumor would suffice in patients with tumor-free lymph nodes. The majority of the papers on esophageal and gastric nodes. The majority of the papers on esophageal and gastric cancer come from Japan, but it can be expected that Europe and the US will follow suit soon. Regarding colon cancer, lymph node status remains the most important prognostic factor in regards to disease-free and overall survival. The presence or absence of lymph node metastases largely dictates whether patients should receive adjuvant chemotherapy. Sentinel node biopsy is an accurate and cost-effective method to identify micrometastases in the lymph nodes.

CONCLUDING REMARKS
Lymphatic mapping with sentinel node biopsy is one of the most interesting developments in clinical oncology in the past decade. This approach allows removal of lymph nodes at risk of harboring metastasis even in locations otherwise not considered. A selection of patients identified as having lymph node metastasis can be treated in an early phase without submitting other patients to unnecessary regional lymph node dissections. Therefore, lymphatic mapping fits in perfectly with the current trend for more conservative surgery in cancer patients. Application in more and more other tumors is being attempted. The long-term safety and effectiveness of lymphatic mapping in clinical practice still need to be proven. Current and future studies will address these issues.

REFERENCES


