Technical aspects, implications, and innovations of the sentinel lymph node biopsy in breast cancer

Chapter 10

Impact paragraph

In the Netherlands approximately 18.000 patients are diagnosed with primary breast cancer each year. Most of these patients have no axillary nodal involvement and will undergo a sentinel lymph node biopsy for axillary staging. In this thesis, we describe different de-escalating strategies and a novel diagnostic procedure for performing sentinel node biopsy, and clarify the evolving adjustments implemented in daily practice. And we discuss the relevance of these adaptations for the different stakeholders.

WHO BENEFITS FROM CHANGING THE LYMPHOSCINTIGRAPHY PROTOCOL?

The standard ^{99mTc} lymphoscintigraphy, applied to detect the sentinel lymph nodes preoperatively , is completed in a two-day setting i.e., the first lymphoscintigraphy on the day before and the second on the day of the surgery. In the COVID-19 pandemic, the lymphoscintigraphy on the second day was omitted, the so- called one-day protocol, to restrict contact between patients and healthcare workers. The results of a retrospective analysis showed no significant differences in detection rates of the sentinel nodes between the two protocols and this approach was considered feasible. In the one-day protocol, only a single lymphoscintigraphy is required, and patients need to visit the nuclear department once, making it a more convenient and patiently friendly approach. Moreover, on the day of surgery, patients are admitted directly to the surgical ward, skipping a visit to the nuclear department, leading to more straightforward planning without the common logistical nuisances between the two departments. By avoiding the second lymphoscintigraphy, the nuclear diagnostic work-up is easier, and the workload on personnel of the nuclear department is downsized. Moreover, this protocol tackles ongoing issues such as the limited availability of healthcare workers, and the restricted capacity of the nuclear department and isotopes. Surgical planning of sentinel node procedures becomes independent of the availability of the nuclear department and thus the number of surgical procedures each day can be enhanced. It is anticipated that the one-day lymphoscintigraphy, by reducing one nuclear assessment, not only facilitates planning but also reduces costs and diminishes the need for manpower. A cost-analysis was not incorporated in the current study but may be of interest for further research. A one-day protocol can be introduced as the standard of care in every breast cancer clinic without any drawbacks.

WHAT IS THE RELEVANCE OF THE ONE-STEP NUCLEIC ACID AMPLIFICATION (OSNA) TECHNIQUE IN CLINICALLY NODE NEGATIVE PATIENTS?

The one-step nucleic acid amplification (OSNA) method is a molecular technique to assess the sentinel lymph nodes, applying the quantitative measurement of target cytokeratin 19 (CK19) mRNA. In our clinic we apply this technique as the standard procedure for years. In nearly 80% of clinically node negative patients the sentinel node biopsy is benign, and since the OSNA provides a prompt perioperative result, these patients can be reassured directly after the procedure. And it also decreases their postoperative distress of waiting on the definitive result, even in cases where metastases are detected. Using the OSNA facilitates a consecutive axillary dissection in case a macrometastasis is found, thereby avoiding a second surgical procedure. However, in cases of breast conserving treatment and pathological nodal involvement, axillary dissection has been replaced by radiation therapy, and the (surgical) importance of obtaining a direct OSNA result can be discussed. Following mastectomy, optimal adjuvant axillary treatment regimens i.e., dissection versus radiation therapy are still under debate and therefore the OSNA method is still of value. Another advantage worth mentioning is that the OSNA examines the whole node with the use of an automated technique, and avoids the time-consuming histological process of staining, multilevel sectioning, and assessment of nodes by the laboratory technician and pathologist, consequently diminishing the workload for the pathology department. With the OSNA, a highly accurate technique, more micrometastasis are detected as shown in our results and although speculated, it did not lead to more adjuvant systemic and radiation therapy. However, the oncological impact of micrometastasis is still unclear, and long-term results on recurrence or survival of patients with micrometastasis, were not the scope of our research, but could be of future interest.

WHAT IS THE ROLE OF THE OSNA IN POSTMASTECTOMY RADIATION THERAPY (PMRT) AND BREAST RECONSTRUCTION?

In the Netherlands approximately 6.000 patients undergo mastectomy annually and the demand for direct breast reconstruction is increasing. Patients, as well as surgeons, aim for the best cosmetic outcome achievable, thus averting postoperative complications seems imperative. One of the acknowledged

risk factors for complications is postmastectomy radiation therapy (PMRT), often indicated when there is pathological involvement of the sentinel node. With the OSNA technique a direct perioperative result is obtained, and if a macrometastasis is detected, the surgeon can decide to postpone a planned direct breast reconstruction to reduce complication risk. However, our observational study showed that the decision about completing PMRT is often more complex, as was demonstrated that numerous patients in whom breast reconstruction was cancelled due to pathological nodal involvement, did not undergoing PMRT in the end. As patients tend to decline a delayed reconstruction as time lapses, the prior described strategy seems debatable. Therefore, it is recommended to define indications for PMRT and the role of the OSNA more accurately in our preoperative multidisciplinary team meeting (MDT) to optimize the option and timing of a breast reconstruction. Recent studies by others proved that PMRT after the placement of a permanent (subcutaneous) implant is associated with low complication rates, and this direct type of reconstruction method could be a safe option independent of the outcome of the sentinel node.

WHY AND HOW TO INTRODUCE A MAGNETIC PROCEDURE FOR SENTINEL NODE BIOPSY?

The use of radioisotopes of the standard ^{99m}Tc lymphoscintigraphy for sentinel node biopsy is associated with strict rules concerning handling, tracking, and disposing of nuclear products and waste, constraining the nuclear and surgical personnel. The non-ionizing technique uses magnetic material, thereby avoiding these logistical issues, and facilitating the scheduling of sentinel node biopsies. In our daily practice, this led to a flatter distribution of patients in the operation--program. It also increased the number of patients treated in day care thanks to the improved availability of day care beds when spread more evenly over the week. In the magnetic procedure, a superparamagnetic iron oxide (SPIO) tracer is injected to identify the sentinel nodes and if required a magnetic seed is placed to localize the non-palpable tumour. The tracer and seed are placed in the radiology department in one session and patients visit the hospital just once, making their planning efficient and more patient friendly. Compared to the use of ^{99m}Tc lymphoscintigraphy, the time frame between tracer injection (SPIO) and surgery widens up from 1 day to 7 -21 days, leading to a less strict planning of the sentinel node procedures. Moreover, the number of surgical procedures is unlimited, as the surgical planning is independent of the capacity of the nuclear staff/department, leading to a

more efficient surgical scheduling. Moreover, in a time of increasing demand for nuclear techniques, and limited availability of radioisotopes, this magnetic technique, avoiding the use of radioactive material, is a durable solution. In this thesis, we described our start-up with this technique and presented the pitfalls and solutions concerning the tracer injection site and doses, and the location of the seeds in a clear layout, which can be used as an instruction manual for implementation. The results of our study were reassuring and at this moment we perform this technique in all patients undergoing a sentinel node procedure as a standard procedure. Future research will concentrate on detection rates of the sentinel nodes and potential complications of the procedure after more than a year of experience.

DOES SPIO TRACER CHANGE THE FOLLOW-UP FOR BREAST CANCER?

After injection of the SPIO tracer, iron particles are left behind in the breast, causing local artefacts potentially interfering with MRI in the future. These artefacts can impede the detection of locally recurrent disease in the follow-up after breast cancer treatment. During the follow-up, an annual standard (FFDM) mammography is recommended to detect potential (local) recurrent disease, and if a complementary investigation is needed, contrast-enhanced mammography (CEM) or breast magnetic resonance image (MRI) is advised. Results of our study showed no disturbances in FFDM and CEM after SPIO injection at approximately one-year follow-up, however all images of the breast magnetic resonance image (MRI) were locally distorted at the tracer sites. Although the risk of local recurrence after breast cancer treatment is low in the first year, and indications for breast MRI during follow-up limited, this finding contributes to the awareness of the radiologist when evaluating MRI images, that they will face artefacts after the use of magnetic tracer for axillary staging. Since CEM showed no abnormalities after SPIO injection, and earlier studies demonstrated that CEM is highly accurate in detecting recurrent disease, CEM could be the first choice of imaging modality if additive information is needed. Further studies will focus on the role of CEM in the neoadjuvant setting in evaluating response, and on the evaluation of the impact of a non-ionized seed in the assessments of CEM images. Another topic of further interest could be the evaluation of the effect of SPIO tracer in breast MRI after a longer period, as radiological interference of the iron particles diminishes over time.

FUTURE PERSPECTIVES

We are confident that this thesis creates sufficient ground for further research and several suggestions are made. At this moment we collect the data of the sentinel lymph node biopsies after the SPIO tracer injection in a larger cohort to compare the outcome with the results of our previous studies. At this moment, we just completed a feasibility study investigating the effect of non-ionizing magnetic seeds in CEM images (CEMMAG study, METCZ2022016) in patients with non-palpable breast tumours. And we hope to start off with a study to investigate if magnetic seed placement at the start of the neoadjuvant therapy disturbs the response monitoring with CEM during treatment. With this thesis we also proved that the need for nuclear procedures and products in breast cancer surgery can be reduced significantly, in time of increasing demand for radioisotopes and rising health care costs, these alterations keep breast cancer treatment lean and mean.