

Article

Accuracy of Magnetometer-Guided Sentinel Lymphadenectomy after Intraprostatic Injection of Superparamagnetic Iron Oxide Nanoparticles in Prostate Cancer: The SentiMag Pro II Study

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Abstract: Targeted radioisotope-guided sentinel lymph node dissection (sLND) has shown high diagnostic accuracy in prostate cancer (PCa). To overcome the downsides of the radioactive tracers, magnetometer-guided sLND using superparamagnetic iron oxide nanoparticles (SPIONs) was successfully applied in PCa. This prospective study (SentiMag Pro II, DRKS00007671) determined the diagnostic accuracy of magnetometer-guided sLND in intermediate- and high-risk PCa. Fifty intermediate- or high-risk PCa patients (PSA \geq 10 ng/ml and/or Gleason score \geq 7; median PSA 10.8 ng/ml, IQR 7.4–19.2 ng/ml) were enrolled. After intraprostatic SPIONs injection a day earlier, patients underwent magnetometer-guided sLND and eLND, followed by radical prostatectomy. SLNs were detected in vivo and in ex vivo samples. Diagnostic accuracy of sLND was assessed using eLND as the reference. SLNs were detected in all patients (detection rate 100%), with 447 SLNs (median 9, IQR 6–12) being identified and 966 LNs (median 18, IQR 15–23) being removed. Thirty-six percent (18/50) of patients had LN metastases (median 2, IQR 1–3). Magnetometer-guided sLND had 100% sensitivity, 97.0% specificity, 94.4% positive predictive value, 100% negative predictive value, 0.0% false negative rate, and 3.0% additional diagnostic value (LN metastases only in SLNs outside the eLND template). In vivo, one positive SLN/LN-positive patient was missed, resulting in a sensitivity of 94.4%. In conclusion, this new magnetic sentinel procedure has high accuracy for nodal staging in intermediate- and high-risk PCa. The reliability of intraoperative SLN detection using this magnetometer system requires verification in further multicentric studies.

Keywords: lymphadenectomy; magnetometer; prostate cancer; sentinel lymph node dissection; SPION; superparamagnetic iron oxide nanoparticles

1. Introduction

Pelvic lymph node (LN) dissection (LND) is still the gold standard for LN staging in clinically localized prostate cancer (PCa). The prevalence of LN involvement is directly related to the number of dissected LNs or the extent of the LND [1]. However, the rate of complications rises along with the number of LNs removed [2].

Because of the therapeutic consequences and morbidity of extended LND (eLND), as well as the low detection rate of limited LND techniques, Wawroschek et al transferred the concept of targeted radioisotope-guided sentinel LN (SLN) identification used in other tumor entities to PCa [3]. The conventional use of radioisotope-guided SLN identification in PCa patients involves radioactive marking of SLNs with ^{99m}Techetium nanocolloid and a gamma probe for intraoperative SLN detection. In a systematic literature review, the diagnostic accuracy of this sentinel-guided LN dissection (sLND) approach was determined by evaluating data from 21 studies (2509 patients) [4]. The findings revealed that the diagnostic accuracies of eLND and targeted sLND were almost the same. Moreover, it was demonstrated that sLND yielded higher LN invasion (LNI) rates in sentinel cohorts than were expected from established nomograms [5–7].

Nevertheless, because of the ionizing radiation emitted by the technetium-based tracer material, the advantages of the current SLN procedure are accompanied by some drawbacks. The dependence on radioisotopes or nuclear medicine facilities limits the application of this procedure to small parts of the developed world, and imposes restrictions on patient planning and hospital logistics. Moreover, the procedure exposes patients and surgical staff to ionizing radiation. To overcome these limitations, superparamagnetic iron oxide nanoparticles (SPIONs) have been successfully used to identify SLNs in breast cancer patients [8]. In a pilot study, we presented the first results on the intraoperative identification of SLNs in PCa patients using a handheld magnetometer after intraprostatic SPIONs injection, and demonstrated the feasibility and safety of this new magnetic SLN detection procedure in PCa [9].

In view of these findings, we hypothesized that magnetometer-guided sLND would have high reliability in the detection of LN-positive PCa patients, being comparable with the radioisotope-guided sentinel approach.

To assess the diagnostic accuracy of magnetometer-guided sLND in PCa, this prospective single-center study analyzed intermediate- and high-risk PCa patients who underwent magnetometer-guided sLND and eLND, followed by radical retropubic prostatectomy. The diagnostic accuracy of magnetometer-guided sLND was determined using eLND as the reference standard.

2. Results

As planned, the study included 50 intermediate- or high-risk PCa patients who underwent radical retropubic prostatectomy with magnetometer-guided sLND after intraprostatic injection of SPIONs, with eLND being performed as the reference standard. Table 1 summarizes the patient characteristics.

82

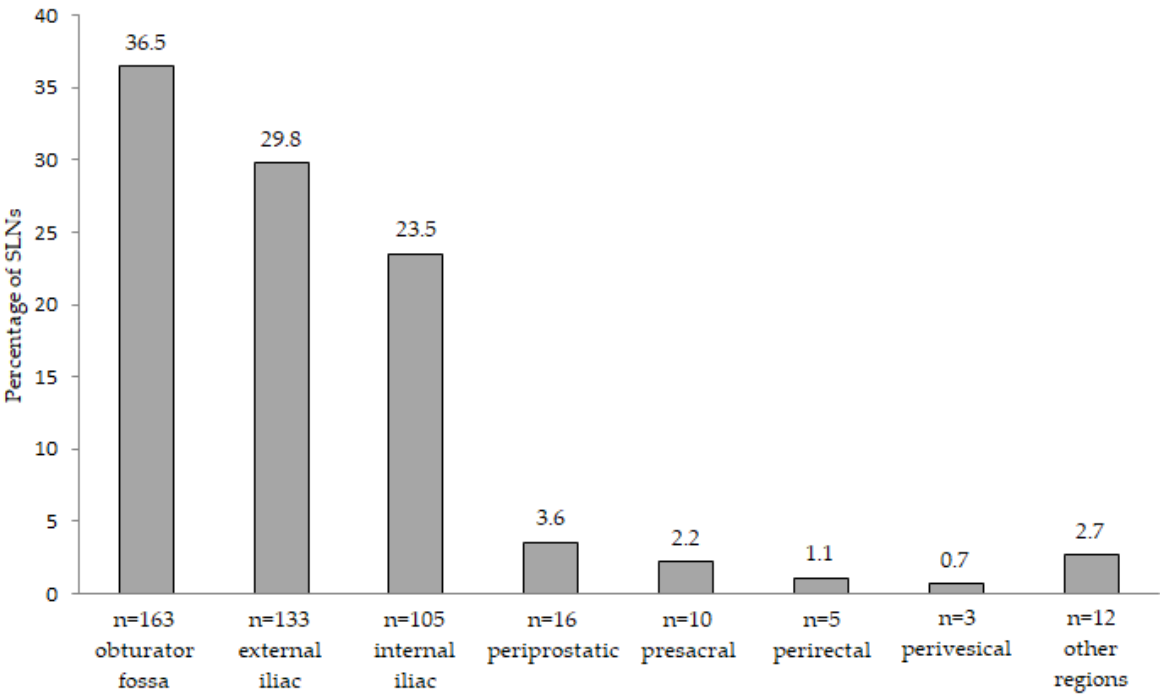
Table 1. Patient characteristics

	Overall n=50	Patients with negative LNs n=32 (64%)	Patients with positive LNs n=18 (36%)
Age, years (median)	69.5	68.5	71.5
IQR	64-73	64-73	64.5-73
Total PSA, ng/ml (median)	10.8	9.8	12.0
IQR	7.4-19.2	6.9-14.7	8.3-30.1
No. of LNs removed (median)	18	19	17.5
IQR	15 -23	15-23	16 -22
No. of SLNs removed (median)	9	9	10
IQR	6-12	5-11	7-12
No. of positive LNs (median)			2
IQR			1-3
Tumor stage (%)			
T1c	28 (56)	22 (68.8)	6 (33.3)
T2a	2 (4)	1 (3.1)	1 (5.6)
T2b	6 (12)	4 (12.5)	2 (11.1)
T2c	12 (24)	5 (15.6)	7 (38.9)
T3	2 (4)	0 (0)	2 (11.1)
Biopsy Gleason score (%)			
6 (3+3)	8 (16)	8 (25.0)	0 (0)
7 (3+4)	26 (52)	18 (56.3)	8 (44.4)
7 (4+3)	6 (12)	5 (15.6)	1 (5.6)
≥8	10 (20)	1 (3.1)	9 (50.0)
Postoperative Gleason score (%)			
6 (3+3)	2 (4)	2 (6.3)	0 (0)
7 (3+4)	23 (46)	19 (59.4)	4 (22.2)
7 (4+3)	14 (28)	8 (25.0)	6 (33.3)
≥8	11 (22)	3 (9.4)	8 (44.4)
Pathologic stage (%)			
pT2	24 (48)	22 (68.8)	2 (11.1)
pT3a	12 (24)	7 (21.9)	5 (27.8)
pT3b	12 (24)	3 (9.4)	9 (50.0)
pT4	2 (4)	0 (0)	2 (11.1)

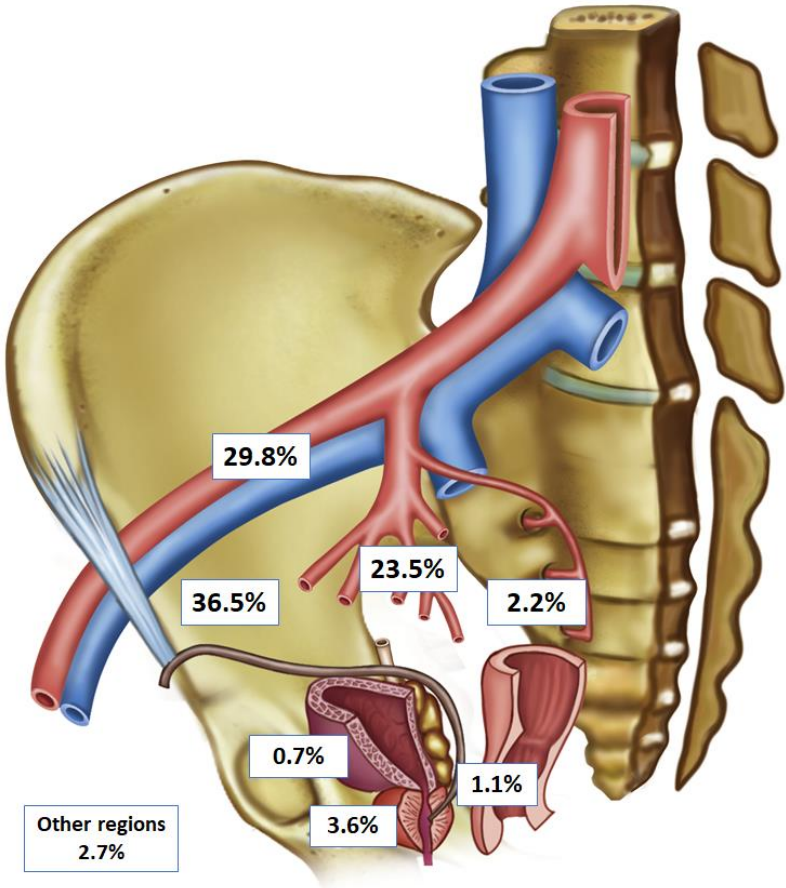
IQR, Interquartile range; (S)LN, (sentinel) lymph node; PSA, prostate specific antigen

In all, 966 LNs (median 18 per patient, IQR 15–23) were removed. At least one SLN was successfully detected by magnetometer-guided sLND in all patients (50/50), resulting in a detection rate of 100%. According to the ex vivo measurements of magnetic LN activity, a total of 447 SLNs were identified. The median number of detected SLNs was 9 (IQR 6–12).

SLNs were also localized outside the established eLND template (e.g., the periprostatic region: 3.6%; presacral region: 2.2%). Figure 1 shows the detailed distributions of all SLNs per anatomical region.



(a)



(b)

Figure 1. (a) Anatomical distribution of the 447 prostate sentinel lymph nodes from the 50 intermediate- or high-risk patients based on magnetometer-guided detection after intraprostatic injection of superparamagnetic iron oxide nanoparticles. (b) Distribution and localization of sentinel nodes in an anatomical pelvic model.

LN metastases were found in 36% (18/50) of patients. In total, 43 LNs were metastasis positive, with the median number of positive nodes (when present) being 2 (IQR 1–3). Taking eLND as the reference standard, the sensitivity of the magnetic SLN procedure was 100%, i.e. all patients with LN metastases were correctly detected as LN-positive. The magnetometer-guided sLND results had a specificity of 97.0%, positive predictive value (PPV) of 94.4%, and negative predictive value (NPV) of 100%, resulting in a false negative rate of 0.0%. sLND was shown to be of additional diagnostic value in one of the 18 LN-positive patients. In this case, sLND resulted in the detection of one LN metastasis outside the eLND template (presacral), while eLND did not reveal any metastases (false positive rate 3%). Figure 2 shows the distribution of all detected LN metastases per anatomical region.

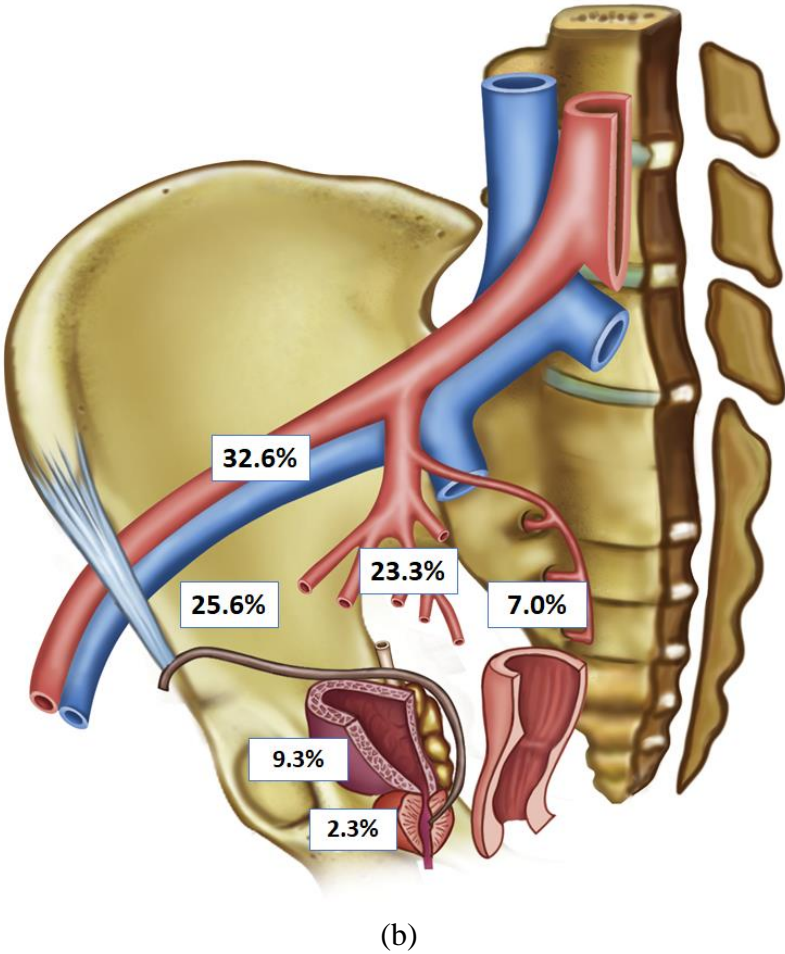
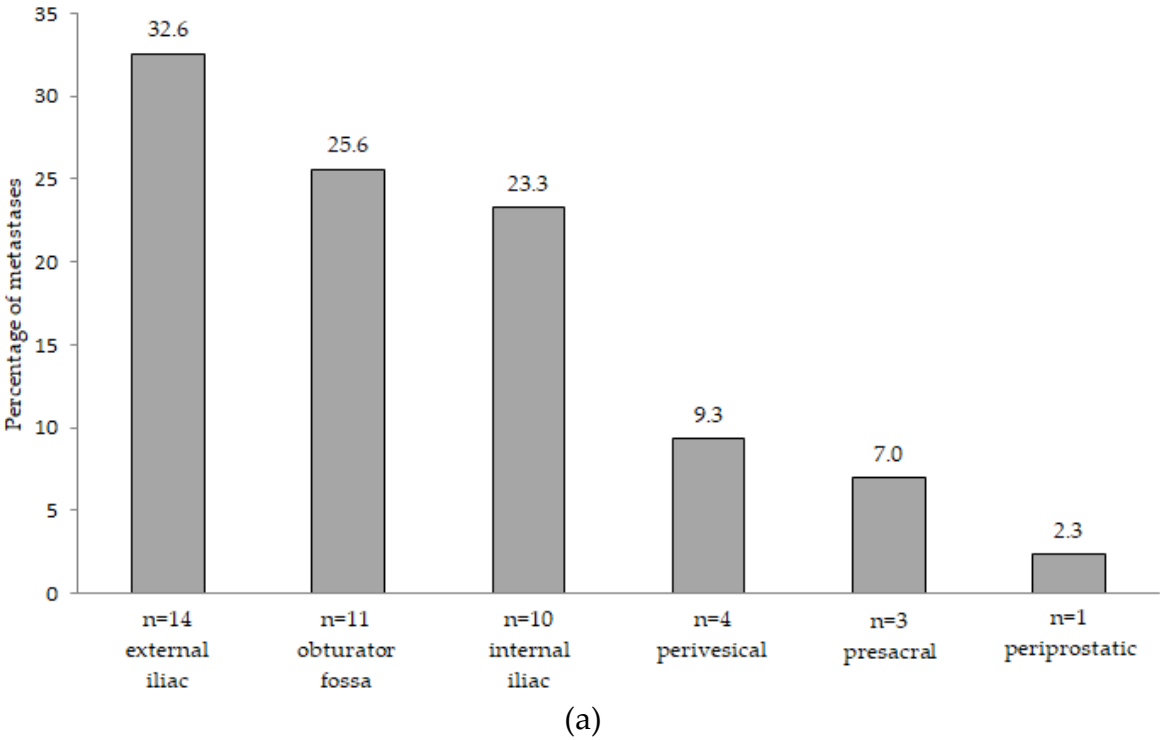


Figure 2. (a) Areas and anatomical distribution of lymph node metastases (n=43) detected by extended pelvic lymph node dissection and/or magnetometer-guided sentinel lymphadenectomy after intraprostatic injection of superparamagnetic iron oxide nanoparticles in 18 lymph node-positive patients with intermediate- or high-risk prostate cancer. (b) Distribution and localization of lymph node metastases in an anatomical pelvic model.

The percentage of LN-positive patients with metastases only in SLNs was 77.8% (n = 14). Intraoperative measurement of magnetic activity or detection of SLNs using the handheld magnetometer missed one LN-positive patient in whom one positive SLN was not detected, resulting in a sensitivity of 94.4% (17/18).

3. Discussion

After the successful application of sentinel diagnostics in breast cancer, the feasibility and safety of intraoperative detection of SLNs using intraprostatic SPION injection and a handheld magnetometer was demonstrated in PCa [9]. Currently, the use of this magnetic sentinel procedure is also being investigated in other tumor entities; for example, initial positive results have recently been shown for penile cancer [10].

On the basis of results comparable to the radioactive marking of SLNs in breast cancer and the promising first results presented in our PCa pilot study (SentiMag Pro I) [8, 9, 11], we hypothesized that magnetometer-guided sLND would also have high reliability in the identification of SLNs or LN-positive PCa patients, being comparable to the radioisotope-guided sentinel approach.

In the results presented for the SentiMag Pro II trial, which included PCa patients with an intermediate- or high-risk for the presence of lymphatic metastasis, SLNs were identified in all patients, resulting in a detection rate of 100%. This is better than in our pilot study that included PCa patients with the same risk factors, where the magnetic technique successfully identified SLNs in only 89.5% of cases [9]. For radioisotope-guided sLND, Holl et al. showed a detection rate of 98.0% in a study including over 2000 low-, intermediate-, and high-risk PCa patients [12]. One meta-analysis revealed a pooled detection rate of 93.8% for radio-guided sLND [13], while a systematic literature review considering 21 studies recruiting 2509 patients found a median cumulative percentage detection rate of 95.9% (IQR 89.4–98.5%) [4]. However, in the SentiMag Pro II study, we adjusted the exclusion criteria according to some of the fundamental limitations of sLND already described by us and others (e.g., previous hormonal treatment or prostate surgery), which may have improved our detection rate [9].

In the ex vivo analysis using the handheld magnetometer to identify SLNs, all LN-positive patients were correctly detected in the SentiMag Pro II study. However, one metastatic SLN was not detected intracorporeally using the SentiMag probe, resulting in the missing of one LN-positive patient and a sensitivity of 94.4%. In the systematic literature review mentioned above, the median cumulative percentage results for sLND showed a sensitivity of 95.2% (81.8–100%) and false negative rate of 4.8% (0–18.2%), taking into account in vivo SLN identification [4]. Accordingly, the SentiMag Pro II results can be considered comparable, and indicate that the use of intraprostatically injected SPIONs combined with intraoperative use of a handheld magnetometer forms a reliable replacement for the radioactive approach in PCa patients.

There are various possible causes limiting the effectiveness of intracorporeal detection of SPION-marked SLNs using a magnetometer. Intracorporeally, adipose tissue surrounding SLNs can limit the proximity of the probe to the node, resulting in insufficient exposure of the node or insufficient measurement of the magnetic signal. Furthermore, the presence of tissue in the vicinity of the probe tip reduces the in vivo magnetic signal because of the negative magnetic susceptibility of surrounding tissue [14]. The limited spatial resolution of the SentiMag® probe (~20 mm) could restrain the differentiation of SLN signals from the background signal from the injection site; however, the higher resolution of novel probes using magnetic tunneling junction techniques (resolution ~4 mm) could lead to an improvement in intraoperative SLN detection [14]. In addition, the now available possibility of preoperative localization of magnetically-marked SLNs using magnetic resonance imaging (MRI) could further improve intraoperative detectability [15].

In 22.2% (n = 4) of LN-positive cases, metastases were also found in non-SLNs. All four cases were patients with high aggressive PCa (PSA >40ng/ml, Gleason score ≥ 8), in accordance with previous reports showing poorer outcomes for sLND with highly aggressive tumors [16]. One fundamental problem of the SLN approach is that fully metastasized LNs or blocked lymph pathways can redirect the tracer, as has already been described for lymphatic spread, and LNs not

detected by sLND might already be connected downstream [17]. However, magnetometer-guided sLNA may detect LN metastases outside the established eLND template. For example, in the SentiMag Pro II study, 7% of positive nodes were detected in the presacral region. Joniau et al showed that 7% of preoperatively detected SLNs were found in the presacral region, and 8% of LN-positive patients would have been missed if an LND in the presacral region had not been performed [18]. Thus, if the goal is to remove as many positive LNs as possible and not just SLNs, sLND must be combined with eLND in high-risk PCa patients.

The limitations of this study include those inherent to the selection bias associated with surgical series from a single institution and a small sample size. In terms of limitations, it should be noted that the study center that conducted the SentiMag Pro II trial has a very high level of expertise in sLND approaches, which may have introduced bias. However, the staging accuracy and rates of LNI detected by sLND in the monitored sample compare well with data from other sLND series [4]. To overcome these limitations, multicenter studies with a larger number of cases should be performed. In addition, a direct comparison of the new magnetic procedure with the radioisotope-guided approach, which can be accomplished by injecting both tracers, as performed by others in breast cancer patients, would be desirable [8, 19]. However, our ethics committee did not allow us to perform this in the SentiMag Pro II study.

4. Materials and Methods

4.1. Study design and patients

The prospective monocentric SentiMag Pro II study (German Clinical Trials Register: DRKS00007671) investigated the diagnostic accuracy of a novel technique for intraoperative SLN detection in PCa patients, using SPIONs and a handheld magnetometer.

Fifty patients with intermediate- or high-risk PCa (European Association of Urology risk group definitions) scheduled for open radical retropubic prostatectomy and pelvic LND between February and September 2015 were included in this study [20]. Inclusion criteria were a PSA level ≥ 10.0 ng/mL and/or a Gleason score ≥ 7 . Exclusion criteria included a known intolerance or hypersensitivity to iron or dextran compounds, iron overload disease, a pacemaker or other implantable device in the chest wall, hormonal treatment, and previous prostate surgery.

4.2. Magnetic SPION tracer

The SPION tracer (Sienna+[®]) used in this study is a component of the SentiMag[®] system (Endomagnetics Ltd., Cambridge, UK). This system for marking and identifying SLNs comprises a handheld magnetometer, the SentiMag[®] unit, and the Sienna+[®] magnetic tracer. All are CE certified as class IIa medical devices. The particles have a carboxydextran coating and a mean hydrodynamic diameter of 60 nm. Sienna+ has comparable functional properties to that of ^{99m}Techetnetium nanocolloid, because upon interstitial injection the tracer flows through the lymph system and gets trapped in SLNs in the same manner as the radionuclide.

4.3. Tracer injection

The sentinel technique in PCa differs from that in other tumor types. In breast cancer and malignant melanoma, a well-directed peritumoral injection is used to observe the lymphatic drainage of the tumor only. In PCa, which commonly occurs as a multifocal malignancy, it is not known with absolute certainty from which part of the organ the metastatic spread originated, or which lesion is the index lesion. Therefore, the aim of prostate lymph scintigraphy must be the imaging of all the primary draining LNs of the prostate, which must therefore include the SLN of the cancer.

In this study, one urologist injected 2 mL of SPION (Sienna+) into the prostate of patients using transrectal ultrasound guidance 24 hours before surgery. Based on our examinations and those of others, the tracer was evenly spread as three deposits on both sides of the prostate in all cases, as described previously [9].

4.4. Magnetometer-Guided sLND, eLND, and histopathological examination

Patients underwent magnetometer (SentiMag)-guided sLND and eLND, followed by radical retropubic prostatectomy. All cases were performed by two high-volume surgeons, who applied the same anatomical template during eLND. The eLND template included the area along the external iliac vessels, with the distal limit being the femoral canal. Proximally, eLND was carried out to, and included, the bifurcation of the common iliac artery. All lymphatic fatty tissue along the internal iliac artery and within the obturator fossa and the area dorsal to the obturator nerve was removed, as described by Weingärtner et al. [21]. The lateral limit consisted of the pelvic sidewall, while the medial dissection limit was defined by the perivesical fat.

During sLND, all metal retractors were removed from the surgical field and polymer retractors (SUSI®, Aesculap®; B. Braun Melsungen AG, Melsungen, Germany) were used to avoid interference with the magnetometer when detecting SLNs with the SentiMag probe. All SLNs detected by the SentiMag were removed, with each magnetically active LN being considered as an SLN. In addition, the magnetic activity of all LNs was measured ex vivo. For surgical reasons, LNs other than SLNs directly adjoining and adhering to SLNs were also removed if in situ separation was not possible. In such cases, LNs were macroscopically detected (tactile and visually) ex vivo and the surgeon separated them from each other or from the containing fibro-fatty tissue. Thereafter, eLND was conducted to remove the remaining lymphatic fatty tissue from the above-named regions. Afterwards, LNs were macroscopically detected and separated from the containing fibro-fatty tissue by the surgeon.

Postoperatively, all LNs were detected and separated by the surgeon (SLNs and non-SLNs), cut into 3-mm transverse sections, and routinely processed and embedded in paraffin, while 4–5-µm-thick sections were further cut and stained with hematoxylin-eosin.

4.5. Outcome Measures of Magnetometer-Guided sLND

As established by our and other working groups, and in line with the results of an international sentinel consensus meeting, the diagnostic accuracy of sLND was assessed using conventional eLND in the same cohort as the reference standard [4, 22]. Compliance with this standard ensures that our results can be compared with the results of other sentinel techniques.

The outcomes used to analyze the diagnostic test accuracy were detection rate (patients with at least one detected SLN/total number of patients operated on), sensitivity, specificity, PPV, NPV, false-positive, and false-negative rates; with all being measured at the patient level. False-negative cases were defined as patients with a histologically negative SLN, whilst cancer was found in other LNs. False-positive cases were defined as patients with SLNs containing metastases found outside the eLND template, while the eLND template did not reveal any metastases [4]. Thus, the false-positive rate provides a measure of the additional diagnostic value of sLND over and above eLND (false-negative on eLND).

A 2 × 2 table with sLND as the index test and eLND as the reference standard was used to calculate sensitivity, specificity, NPV, and PPV. Additionally, the anatomical distributions of detected LN metastases and identified SLNs were analyzed.

4.6. Ethical Approval

All subjects gave their informed consent for inclusion before they participated in the study. The protocol followed in this study was in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. The protocol was approved by the Medical Chamber of Lower Saxony, Germany (Bo/24/2014).

5. Conclusions

The results of this prospective clinical trial suggest that the magnetometer-guided radiation-free sentinel procedure could be a reliable replacement for the established radioisotope-based approach in PCa patients who are at intermediate- or high-risk for LN involvement. With the aim of detecting

all LN metastases in high-risk patients, sLND should be performed in addition to eLND, because of its additional diagnostic value and the detection of LN metastases outside the extended template. The reliability of intraoperative SLN detection using the SentiMag system requires verification in further multicentric studies, including comparisons with other new magnetometer modalities.

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