

1 Article

2 Accuracy of Magnetometer-Guided Sentinel 3 Lymphadenectomy after Intraprostatic Injection of 4 Superparamagnetic Iron Oxide Nanoparticles in 5 Prostate Cancer: The SentiMag Pro II Study

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

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

43 **1. Introduction**

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

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

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

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

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

75 **2. Results**

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

80
81

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)

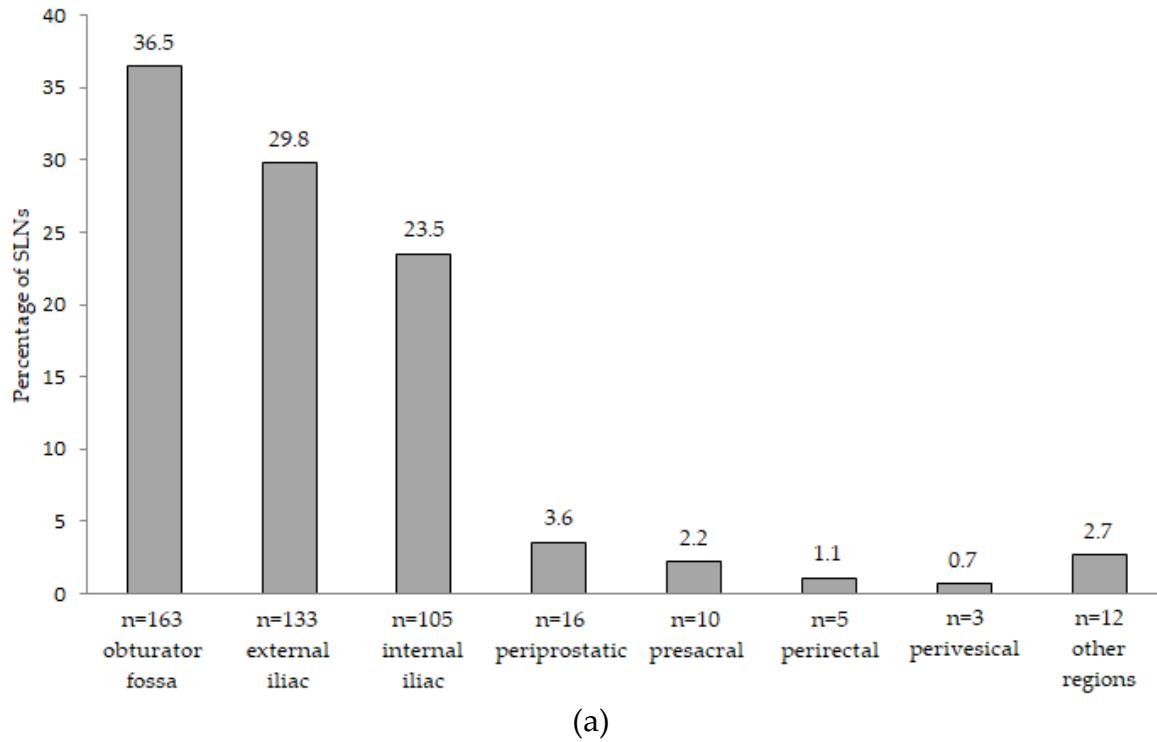
83 IQR, Interquartile range; (S)LN, (sentinel) lymph node; PSA, prostate specific antigen

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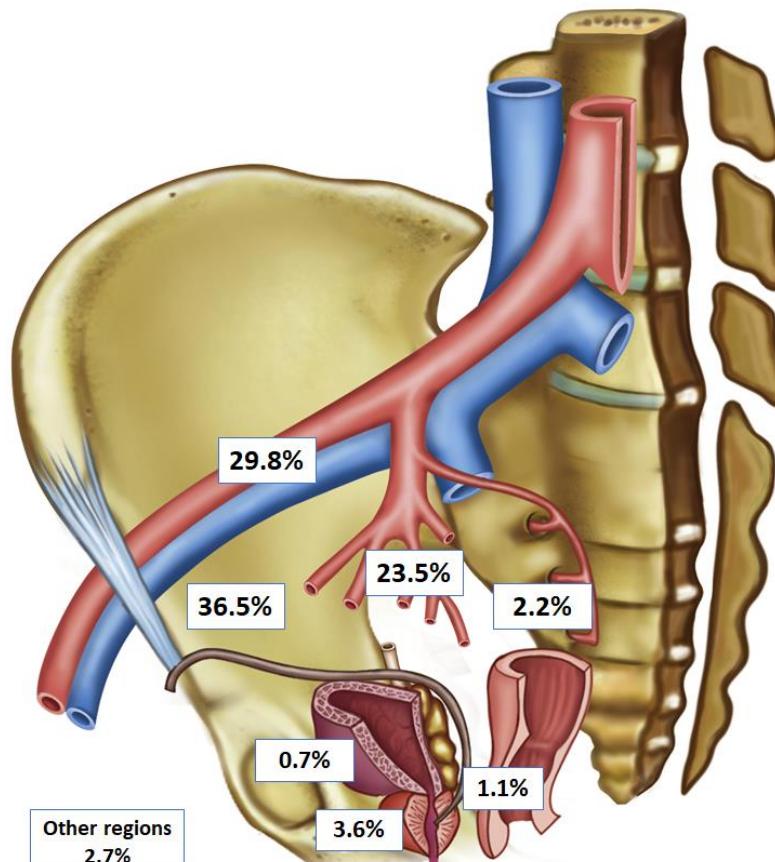
85 In all, 966 LNs (median 18 per patient, IQR 15-23) were removed. At least one SLN was
 86 successfully detected by magnetometer-guided sLND in all patients (50/50), resulting in a detection
 87 rate of 100%. According to the ex vivo measurements of magnetic LN activity, a total of 447 SLNs
 88 were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

89 SLNs were also localized outside the established eLND template (e.g., the periprostatic region:
 90 3.6%; presacral region: 2.2%). Figure 1 shows the detailed distributions of all SLNs per anatomical
 91 region.

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(a)



(b)

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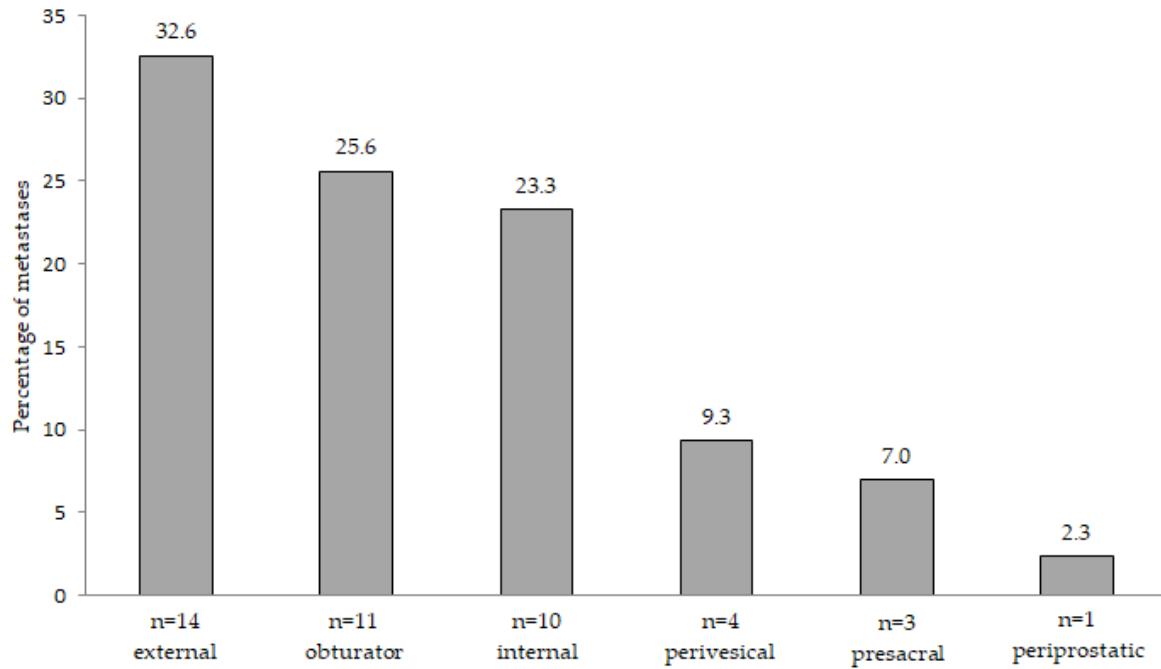
Figure 1. (a) Anatomical distribution of the 447 prostate sentinel lymph nodes from the 50 intermediate- or high-risk patients based on magnetometer-guided detection after intraprostatic injection of superparamagnetic iron oxide nanoparticles. (b) Distribution and localization of sentinel nodes in an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

98 LN metastases were found in 36% (18/50) of patients. In total, 43 LNs were metastasis positive,
99 with the median number of positive nodes (when present) being 2 (IQR 1–3). Taking eLND as the
100 reference standard, the sensitivity of the magnetic SLN procedure was 100%, i.e. all patients with LN
101 metastases were correctly detected as LN-positive. The magnetometer-guided sLND results had a
102 specificity of 97.0%, positive predictive value (PPV) of 94.4%, and negative predictive value (NPV) of
103 100%, resulting in a false negative rate of 0.0%. sLND was shown to be of additional diagnostic value
104 in one of the 18 LN-positive patients. In this case, sLND resulted in the detection of one LN metastasis
105 outside the eLND template (presacral), while eLND did not reveal any metastases (false positive rate
106 3%). Figure 2 shows the distribution of all detected LN metastases per anatomical region.

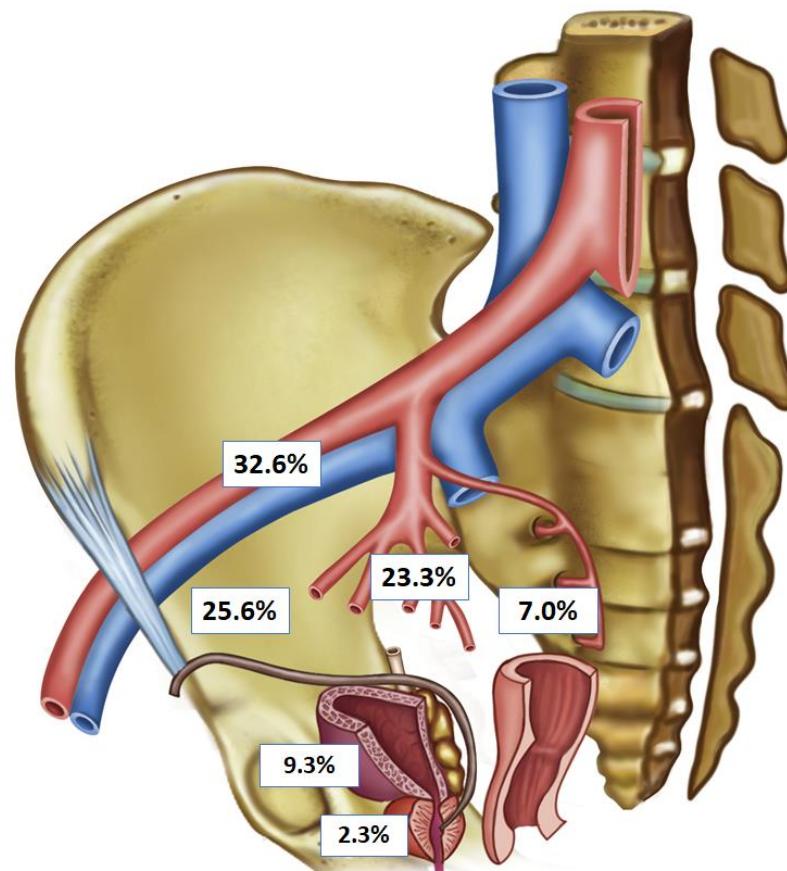
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(a)



(b)

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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.

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

119 **3. Discussion**

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

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

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

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

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

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

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

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

183 4. Materials and Methods

184 4.1. Study design and patients

185 The prospective monocentric SentiMag Pro II study (German Clinical Trials Register:
186 DRKS000007671) investigated the diagnostic accuracy of a novel technique for intraoperative SLN
187 detection in PCa patients, using SPIONs and a handheld magnetometer.

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

194 4.2. Magnetic SPION tracer

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

202 4.3. Tracer injection

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

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

213

214 **4.4. Magnetometer-Guided sLND, eLND, and histopathological examination**

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

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

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

236 **4.5. Outcome Measures of Magnetometer-Guided sLND**

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

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

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

252 **4.6. Ethical Approval**

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

257 **5. Conclusions**

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

261 all LN metastases in high-risk patients, sLND should be performed in addition to eLND, because of
262 its additional diagnostic value and the detection of LN metastases outside the extended template.
263 The reliability of intraoperative SLN detection using the SentiMag system requires verification in
264 further multicentric studies, including comparisons with other new magnetometer modalities.
265

266 **Author Contributions:** Conceptualization, Alexander Winter, Stefan Gudenkauf and Friedhelm Wawroschek;
267 Data curation, Svenja Engels, Philipp Goos and Marie-Christin Süykers; Formal analysis, Alexander Winter and
268 Svenja Engels; Funding acquisition, Alexander Winter; Investigation, Alexander Winter, Svenja Engels, Philipp
269 Goos, Marie-Christin Süykers, Rolf-Peter Henke and Friedhelm Wawroschek; Methodology, Alexander Winter
270 and Friedhelm Wawroschek; Project administration, Svenja Engels, Philipp Goos and Marie-Christin Süykers;
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