Simplified intraoperative sentinel-node detection performed by the urologist accurately determines lymph-node stage in prostate cancer.

Kjölhede, Henrik; Bratt, Ola; Gudjonsson, Sigurdur; Sundqvist, Pernilla; Liedberg, Fredrik

Published in:
Scandinavian Journal of Urology

DOI:
10.3109/21681805.2014.968867

2015

Simplified intraoperative sentinel node detection performed by the urologist accurately determines lymph node stage in prostate cancer

Henrik Kjölhede[1], Ola Bratt[2], Sigurdur Gudjonsson[3], Pernilla Sundqvist[4], Fredrik Liedberg[3]

1 Department of Surgery, Växjö Hospital, Lund University, Sweden

2 Department of Urology, Helsingborg Hospital, Lund University, Sweden

3 Department of Urology, Skåne University Hospital, Lund University, Sweden

4 Department of Urology, Örebro University Hospital, Sweden

Running head: Sentinel node in prostate cancer

Corresponding author:
Henrik Kjölhede, Department of Surgery, Växjö Hospital, SE-351 85 Växjö, Sweden
Tel: +46-702-988922
E-mail: henrik.kjolhede@med.lu.se

Manuscript includes
2374 words and abstract 248 words, 3 tables

Keywords: Prostate Cancer, Lymph Node Staging, Sentinel Lymph Node Biopsy, Sentinel Node, Extended Serial Sectioning, Immunohistochemistry

Abstract

Objective: The reference standard for lymph node staging in prostate cancer is currently an extended pelvic lymph node dissection (ePLND), which detects the majority, but not all, of regional lymph node metastases. As an alternative to ePLND, sentinel node (SN) dissection with preoperative isotope injection and imaging has been reported. The objective was to determine whether intraoperative SN detection with a simplified protocol can accurately determine lymph node stage in prostate cancer patients.

Materials and methods: Patients with biopsy-verified high-risk prostate cancer with tumour stage T2-3 were included in the study. All patients underwent both ePLND and SN detection. ^{99m}Tc-marked nanocolloid was injected peritumourally by the operating urologist after induction of anaesthesia just prior to surgery. SNs were detected both in-vivo and ex-vivo intraoperatively using a gamma probe. SNs and metastases and their locations were recorded. Sensitivity and specificity were calculated.

Results: At least one SN was detected in 72 (87%) of the 83 patients. In 13 (18%) of these 72 patients SNs were detected outside the ePLND template. In six of these 13 patients, the SNs from outside the template contained metastases, which proved to be the only metastases in two. For 12 patients the only metastatic deposit found was a micrometastasis (≤ 2 mm) in a SN. In the 72 patients with detectable SNs, pathological analysis of the SNs correctly categorised 71 and ePLND 70 patients.

Conclusions: This protocol yielded results comparable to the commonly used technique of SN detection, but with more cases of non-detection.

Introduction

The absence or presence of lymph node metastases is one of the most important prognostic factors in prostate cancer. The current reference standard for lymph node staging is an extended pelvic lymph node dissection (ePLND), which is recommended in the EAU guidelines for patients with intermediate- or high-risk prostate cancer (1). However, it has been shown that even an ePLND fails to detect up to 13% of lymph node metastases (2). Furthermore, a multimodality lymphatic mapping study has demonstrated primary lymphatic pathways leading directly to lymph nodes of the pararectal and presacral regions, as well as at the aortic bifurcation (3). Including these areas located outside the ePLND template increases lymphadenectomy-associated morbidity, such as thromboembolism and lymphoceles (4). In addition, a more extensive lymph node dissection may worsen potency outcomes in conjunction with bilateral nerve-sparing radical prostatectomy (5), which could be an option for some patients if considered oncologically safe. However, there are also indications that identifying and treating lymph node metastases improves survival rates (6,7).

An alternative to expanding the standard limits of the ePLND when staging prostate cancer is to implement the sentinel node (SN) technique (8–14). The SN technique with radio-navigated surgery enables detection of the lymph nodes that have the highest probability of containing metastases based on the patient's own pattern of primary lymphatic drainage, potentially improving the accuracy of the lymph node staging for individual patients. The lymphotropic radioactive tracer is usually injected into the prostate several hours before

surgery without regard to the location of the cancer (8–14). An alternative to this technique was suggested in a study of breast cancer patients, in which early visualisation of SNs (i.e. less than 30 min after injection) was achieved in a majority of the patients given a higher and optimised dose of tracer (15). Inspired by our experience with such an injection protocol in bladder cancer we intended to investigate a SN technique in prostate cancer patients, with injection of the isotope in proximity to the tumour at the start of surgery, after induction of anaesthesia (16).

The aim of our study was to determine whether the new and simplified protocol for intraoperative SN detection properly identifies SNs and also whether these SNs accurately reflect the lymph node stage.

Materials and methods

Patients and ethical approval

Following a pilot study with five patients in 2004, the study included consecutive patients at Växjö Hospital from April 2007 to May 2012. All patients had biopsy-verified high-risk prostate cancer according to the d'Amico classification and were in clinical stage T2-3 Nx M0. Oral and written informed consent was given. The study was approved by the Research Ethics Review Board of Lund University (EPN LU350/2005 and LU547/2006).

Surgery

Open surgery was conducted in cases subjected to same-session radical prostatectomy, and laparoscopic surgery if subsequent external radiation therapy was planned. All operations were performed with the patient under

general anaesthesia. Immediately before surgery, after induction of anaesthesia, 100 MBq of ^{99m}Tc-marked nanocolloid (NanoColl, GE Healthcare) was injected into the prostate in four 0.25 ml aliquots (100 MBq / ml) under transrectal ultrasound guidance. The injections were given in two different locations on each side, adjacent to the tumour but not into it. In the case of a unilateral tumour, the two injections given on the contralateral side were distributed in the peripheral zone, one near the base and one near the apex. All injections were given by the operating urologist, who selected the injection sites based on palpatory and ultrasonographic findings, combined with the biopsy pathology reports. Ciprofloxacin (750 mg) was administered orally preoperatively as prophylaxis. All procedures, including the ePLND, were performed by at least one member of a team of three surgeons.

The ePLND was performed as described by Heidenreich and co-workers (17). The borders were defined as follows: the medial border by the bladder and internal iliac artery, thus omitting presacral nodes; the lateral border by the lateral aspect of the external iliac artery; the distal border by the inguinal ligament; the proximal border by the ureteral crossing of the common iliac artery, including all the tissue in the obturator fossa. After the dissection on each side, a gamma probe was used to detect residual lymph nodes showing ^{99m}Tc-nanocolloid uptake in the pelvis. The areas above the aortic bifurcation were not examined. Any nodes with such uptake were dissected and sent separately for pathology. At the end of surgery, the ePLND specimens from each side were also examined using the gamma probe to detect SNs; these nodes were removed from the larger specimen and sent separately for pathology. The fatty tissue containing non-SNs from the open ePLNDs was

sent for pathology in three fractions (external iliac, internal iliac and obturator fossa) per side, whereas the laparoscopic ePLNDs were performed with the monoblock technique with the tissue sent en bloc from the left and right sides (18).

Pathology

All specimens were fixed in formalin and embedded in paraffin. Sentinel nodes were cut into 3-mm thick slices, which were embedded separately in paraffin. Each embedded slice was step-sectioned at three levels at 150 µm intervals. All sections were stained with haematoxylin-eosin and anti-cytokeratin antibodies (AE1/AE3). Detected metastases that were ≤ 2 mm in diameter were designated micrometastases.

Statistics

For the patients in whom at least one SN was detected, the VassarStat Clinical Research Calculator was used to compute sensitivity, specificity and negative and positive predictive values with 95% confidence intervals. Reference results were defined by the two methods combined; more precisely, the presence of LN metastases shown by either method was designated node positive, and the absence of LN metastases by both methods was denoted node negative. For all other results only descriptive statistics were used.

Results

A total of 83 patients were included in the study with the characteristics of the patients outlined in Table 1. At least one SN was detected in 72 (87%) and no

SN in 11 (13%) of the patients, 2 of which were operated with open surgery and 9 laparoscopically (8% and 16%, respectively). The SNs were located unilaterally in 26 (31%) patients and bilaterally in 46 (55%). For the 26 patients who underwent open surgery the median number of removed lymph nodes was 19.0 (IQR 14.0-21.5) while the median number of SNs was 2.5 (IQR 2.0-3.25). The 57 patients that were operated laparoscopically had a median of 11.0 (IQR 9.0-15.0) lymph nodes removed and a median of 2.0 (IQR 1.0-3.0) SNs detected.

During intraoperative gamma probe-guided surgery, one or more SNs were detected outside the standard ePLND template in 13 (18%) of the 72 patients (Table 2). In six of these 13 patients, the SNs found outside the template harboured metastases, which would not have been detected by an ePLND. Two patients had their only metastases in a SN outside the standard ePLND template and thus would have been incorrectly classified as N0 by an ePLND.

In one (1.4%) of 72 patients, the SN dissection was negative but the ePLND showed a lymph node metastasis. This patient had a T3 tumour with a Gleason score sum of 9 and a PSA level of 39 µg/l. One SN was detected in this individual, and five more lymph nodes were dissected, one of which was found to contain a 1.2-mm metastasis; this positive lymph node was found on the same side as the SN.

For the 72 patients with detectable SN, compared with the results of the combination of SN dissection and ePLND, the SNs determined lymph node stage with a sensitivity of 0.96 (95% CI, 0.76-1.0), a specificity of 1.0 (95% CI,

0.91-1.0) and a negative predictive value of 0.98 (95% CI, 0.88-1.0) which were all higher than for ePLND alone (Table 3). The SNs contained at least one metastasis in 22 (31%) of the 72 patients and were negative in 50 (69%). When calculating performance for all the 83 patients, sensitivity and negative predictive value were 0.85 (95% CI, 0.64-0.95) and 0.93 (95% CI, 0.83-0.98), respectively.

The overall lymph node positivity was 27% in the open-surgery group and 33% in the laparoscopic group (Table 1). The ePLND detected lymph node metastases in three (27%) of the 11 patients with no detectable SN. Two of these were operated laparoscopically and one was operated with open surgery (4% in both groups).

Of the 26 patients with metastases, 12 (46%) had micrometastases in a SN. For eight (31%) of the 26 patients this represented the only metastatic deposit. Four patients with micrometastases in a SN had additional, larger metastases in another SN. Two of these latter patients had metastases also in the non-SNs. None of the patients where the SNs only detected micrometastases had other metastases in the non-SNs.

Discussion

The SN technique used in our study requires less preoperative workup than the commonly used protocols, but nonetheless yielded similar results regarding the high sensitivity and the ability to detect lymph node metastases outside the template of an ePLND. Weckerman and co-workers reported a

sensitivity of 99% for SN dissection and Meinhardt and colleagues demonstrated a sensitivity of 100% (10,19). SNs were only identified in 87% of the patients, which is a lower proportion than in the cited studies. Whether this is a limitation of this particular protocol or is part of the learning curve of the procedure remains to be determined (13). It is likely that the learning curve is longer for the laparoscopic procedure than the open one, with a higher incidence of non-detection of SNs in our series (16% vs 8%), which needs to be taken into account when doing further studies. In particular, the laparoscopic gamma-probe has a more limited field of detection, which requires a different technique than using a conventional probe in open surgery. Also, the impact of only detecting SNs unilaterally also needs further research. In this study, the addition of intraoperative SN detection to ePLND resulted in the detection of additional metastases in 17% of all the patients where ePLND had detected metastases. Furthermore, 4% of the patients with a negative ePLND were upstaged to N1 as a result of detecting SNs outside the template. This is in line with another recent investigation, which found an additional 6% of patients with lymph node metastases using a combination of preoperative scintigraphy and intraoperative use of a gamma probe for SN detection (2). Holl and co-workers also detected an additional 7% lymph node metastases outside the ePLND template, using SN dissection (8).

It is clear that a more thorough pathological evaluation detects more micrometastases. Extended serial sectioning and immunohistochemistry using anti-cytokeratin antibodies has been shown to increase the detection of metastases that are ≤ 2 mm in diameter (20,21). This has also been illustrated by computer simulations of SNs in breast cancer (22), and confirmed by

another breast cancer study which showed that more extensive pathological analysis alone resulted in a 13% increase in detection of micrometastases (23). Also, real-time PCR was recently reported to increase the detection of micrometastases in 29% of investigated prostate cancer patients (24). Even though the present investigation was not designed to specifically test for increased detection of micrometastases, it is likely that some of the micrometastases identified in 17% of the patients with LN metastases, would have been missed by routine pathology. The value of increased detection of micrometastases is not known, however micrometastases were in two independent studies associated with biochemical recurrence after radical prostatectomy (25,26). Thus, it is possible that a more correct staging, including serial sectioning of SNs, would identify more patients who would benefit from adjuvant therapy (27).

A further development of the SN concept has recently been described by van der Poel and colleagues and Jeschke and co-workers, who independently demonstrated the feasibility of real-time laparoscopic SN detection using a combination of radioisotope and fluorescence guidance (28,29). Jeschke and co-workers have also shown the usefulness of analysing SNs using frozen section in prostate cancer patients (29).

The results of the present and cited studies demonstrate clearly that the sentinel node concept is valid in prostate cancer. Properly identified sentinel nodes accurately reflect the lymph node stage in patients with prostate cancer. Based on this knowledge, a reasonable approach would be to offer all intermediate- and high-risk patients a sentinel node dissection with frozen

section analysis, and perform an ePLND only if the frozen section analysis shows metastases or if no SN is detected. The last point is crucial, since the sensitivity in this study was much lower when taking into account patients with undetected SNs. This setup would be desirable to study further in a large multicentre trial.

A limitation of the current study is that it was not designed to demonstrate whether all SNs could be detected in-vivo during the dissection, i.e. no preoperative imaging was used within the study. However, facilitated in-vivo detection has recently been described by the use of a combination of radioisotope and fluorescence guidance during surgery (28,29), which seems to be a promising direction of future validation. A further limitation in the present study is that en bloc dissection of lymph nodes was done in patients operated laparoscopically, which precluded mapping and a detailed anatomical description of the location of SNs and metastases. It is also possible that the en bloc dissection technique can account for the lower number of removed lymph nodes during laparoscopic surgery as compared to open surgery, when the lymph node specimens were submitted to pathology in three fractions per side (18). Another shortcoming is that the small number of patients included leads to a wide confidence interval for the estimate of the sensitivity of the method. Also, a general limitation of the SN technique is that in some patients with large lymph node metastases, it is not possible to identify the true SNs due to the presence of tumour cells obstructing the lymphatic vessels, causing a re-routing of the lymphatic pathways and thereby false-negative SNs (30).

Conclusions

The simplified protocol for injection and detection of the tracer used in our study yielded results comparable to those reported with the more commonly used SN technique, but a higher number of patients where no SN was detected. Further studies are warranted.

Acknowledgements

This study was funded by grants by FoU Kronoberg, Cancerstiftelsen Kronoberg, and the Swedish Cancer Foundation (grant no. 2012/475).

References

1. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol 2011;59:61–71.

2. Joniau S, Van den Bergh L, Lerut E, Deroose CM, Haustermans K, Oyen R, et al. Mapping of pelvic lymph node metastases in prostate cancer. Eur Urol 2013;63:450–8.

3. Mattei A, Fuechsel FG, Bhatta Dhar N, Warncke SH, Thalmann GN, Krause T, et al. The template of the primary lymphatic landing sites of the prostate should be revisited: results of a multimodality mapping study. Eur Urol 2008;53:118–25.

4. Van Hemelrijck M, Garmo H, Holmberg L, Bill-Axelson A, Carlsson S, Akre O, et al. Thromboembolic events following surgery for prostate cancer. Eur Urol 2013;63:354–63.

5. Sagalovich D, Calaway A, Srivastava A, Sooriakumaran P, Tewari AK. Assessment of required nodal yield in a high risk cohort undergoing extended pelvic lymphadenectomy in robotic-assisted radical prostatectomy and its impact on functional outcomes. BJU Int 2013;111:85–94.

6. Ji J, Yuan H, Wang L, Hou J. Is the impact of the extent of lymphadenectomy in radical prostatectomy related to the disease risk? A single center prospective study. J Surg Res 2012;178:779–84.

7. Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, et al. Predicting Survival of Patients with Node-positive Prostate Cancer Following Multimodal Treatment. Eur Urol (2013), (in press) http://dx.doi.org/10.1016/j.eururo.2013.09.025.

8. Holl G, Dorn R, Wengenmair H, Weckermann D, Sciuk J. Validation of sentinel lymph node dissection in prostate cancer: experience in more than 2,000 patients. Eur J Nucl Med Mol Imaging 2009;36:1377–82.

9. Wawroschek F, Vogt H, Weckermann D, Wagner T, Hamm M, Harzmann R. Radioisotope guided pelvic lymph node dissection for prostate cancer. J Urol 2001;166:1715–9.

10. Weckermann D, Dorn R, Trefz M, Wagner T, Wawroschek F, Harzmann R. Sentinel lymph node dissection for prostate cancer: experience with more than 1,000 patients. J Urol 2007;177:916–20.

11. Corvin S, Schilling D, Eichhorn K, Hundt I, Hennenlotter J, Anastasiadis AG, et al. Laparoscopic sentinel lymph node dissection--a novel technique for the staging of prostate cancer. Eur Urol 2006;49:280–5.

12. Häcker A, Jeschke S, Leeb K, Prammer K, Ziegerhofer J, Sega W, et al. Detection of pelvic lymph node metastases in patients with clinically localized prostate cancer: comparison of [18F]fluorocholine positron emission tomography-computerized tomography and laparoscopic radioisotope guided sentinel lymph node dissection. J Urol 2006;176:2014–8; discussion 2018–9.

13. Warncke SH, Mattei A, Fuechsel FG, Z'Brun S, Krause T, Studer UE. Detection rate and operating time required for gamma probe-guided sentinel lymph node resection after injection of technetium-99m nanocolloid into the prostate with and without preoperative imaging. Eur Urol 2007;52:126–32.

14. Rousseau C, Rousseau T, Bridji B, Pallardy A, Lacoste J, Campion L, et al. Laparoscopic sentinel lymph node (SLN) versus extensive pelvic dissection for clinically localized prostate carcinoma. Eur J Nucl Med Mol Imaging 2012;39:291–9.

15. Valdés-Olmos R a, Jansen L, Hoefnagel C a, Nieweg OE, Muller SH, Rutgers EJ, et al. Evaluation of mammary lymphoscintigraphy by a single intratumoral injection for sentinel node identification. J Nucl Med 2000;41:1500–6.

16. Liedberg F, Chebil G, Davidsson T, Gudjonsson S, Månsson W. Intraoperative sentinel node detection improves nodal staging in invasive bladder cancer. J Urol 2006;175:84–8; discussion 88–9.

17. Heidenreich A, Ohlmann CH, Polyakov S. Anatomical extent of pelvic lymphadenectomy in patients undergoing radical prostatectomy. Eur Urol 2007;52:29–37.

18. Mattei A, Di Pierro GB, Grande P, Beutler J, Danuser H. Standardized and simplified extended pelvic lymph node dissection during robot-assisted radical prostatectomy: the monoblock technique. Urology 2013;81:446–50.

19. Meinhardt W, Valdés Olmos R a, van der Poel HG, Bex A, Horenblas S. Laparoscopic sentinel node dissection for prostate carcinoma: technical and anatomical observations. BJU Int 2008;102:714–7.

20. Wawroschek F, Wagner T, Hamm M, Weckermann D, Vogt H, Märkl B, et al. The influence of serial sections, immunohistochemistry, and extension of pelvic lymph node dissection on the lymph node status in clinically localized prostate cancer. Eur Urol 2003;43:132–6; discussion 137.

21. Fukuda M, Egawa M, Imao T, Takashima H, Yokoyama K, Namiki M. Detection of sentinel node micrometastasis by step section and immunohistochemistry in patients with prostate cancer. J Urol 2007;177:1313–7; discussion 1317.

22. Farshid G, Pradhan M, Kollias J, Gill PG. Computer simulations of lymph node metastasis for optimizing the pathologic examination of sentinel lymph nodes in patients with breast carcinoma. Cancer 2000;89:2527–37.

23. Grabau D, Ryden L, Fernö M, Ingvar C. Analysis of sentinel node biopsy - a single-institution experience supporting the use of serial sectioning and immunohistochemistry for detection of micrometastases by comparing four different histopathological laboratory protocols. Histopathology 2011;59:129–38.

24. Heck MM, Retz M, Bandur M, Souchay M, Vitzthum E, Weirich G, et al. Topography of Lymph Node Metastases in Prostate Cancer Patients Undergoing Radical Prostatectomy and Extended Lymphadenectomy: Results of a Combined Molecular and Histopathologic Mapping Study. Eur Urol (2013), (in press) http://dx.doi.org/10.1016/j.eururo.2013.02.007.

25. Miyake H, Kurahashi T, Hara I, Takenaka A, Fujisawa M. Significance of micrometastases in pelvic lymph nodes detected by real-time reverse transcriptase polymerase chain reaction in patients with clinically localized prostate cancer undergoing radical prostatectomy after neoadjuvant hormonal therapy. BJU Int 2007;99:315–20.

26. Ferrari AC, Stone NN, Kurek R, Mulligan E, McGregor R, Stock R, et al. Molecular load of pathologically occult metastases in pelvic lymph nodes is an independent prognostic marker of biochemical failure after localized prostate cancer treatment. J Clin Oncol 2006;24:3081–8.

27. Kennecke HF, Keyes M. Surgical Management of Node-positive Prostate Cancer: Perspectives from Breast Oncology. Eur Urol (2013), (in press) http://dx.doi.org/10.1016/j.eururo.2013.09.007.

28. Van der Poel HG, Buckle T, Brouwer OR, Valdés Olmos R a, van Leeuwen FWB. Intraoperative laparoscopic fluorescence guidance to the sentinel lymph node in prostate cancer patients: clinical proof of concept of an integrated functional imaging approach using a multimodal tracer. Eur Urol 2011;60:826–33.

29. Jeschke S, Lusuardi L, Myatt A, Hruby S, Pirich C, Janetschek G. Visualisation of the lymph node pathway in real time by laparoscopic radioisotope- and fluorescence-guided sentinel lymph node dissection in prostate cancer staging. Urology 2012;80:1080–6.

30. Weckermann D, Dorn R, Holl G, Wagner T, Harzmann R. Limitations of radioguided surgery in high-risk prostate cancer. Eur Urol 2007;51:1549–56; discussion 1556–8.

Table 1. Demographics of included patients.

	All n=83 (100%)	N0 n=57 (69%)	N1 n=26 (31%)	SN0 n=50 (60%)	SN1 n=22 (27%)	SNx n=11 (13%)
Age (yrs), mean ± SD	65.2 ± 6.3	65.3 ± 6.3	65.2 ± 6.3	65.0 ± 6.4	64.7 ± 6.4	67.7 ± 5.2
PSA (µg/l), mean ± SD	21.1 ± 16.7	19.5 ± 15.1	24.8 ± 19.6	18.2 ± 12.4	23.1 ± 19.4	30.6 ± 24.3
Biopsy Gleason score, n (%)						
5-6	12 (14)	10 (18)	2 (8)	9 (18)	2 (9)	1 (9)
7	44 (53)	35 (61)	9 (35)	29 (58)	8 (36)	7 (64)
8-10	27 (33)	12 (21)	15 (58)	12 (24)	12 (55)	3 (27)
Clinical local tumour stage, n (%)						
T2	22 (27)	19 (33)	3 (12)	16 (32)	3 (14)	3 (27)
T3	61 (73)	38 (67)	23 (88)	34 (68)	19 (86)	8 (73)
% Positive biopsy cores, mean ± SD	59.9 ± 30.2	56.0 ± 29.5	68.6 ± 30.5	56.4 ± 30.3	66.7 ± 30.0	62.2 ± 30.3
No. of lymph nodes, mean (IQR)	14.0 (9.0-18.0)	13.0 (10.0-19.0)	14.0 (8.5-17.25)	14.0 (10.0-19.25)	14.5 (9.75-18.0)	10.0 (9.0-12.0)
No. of sentinel nodes, mean (IQR)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.25)	2.0 (1.75-3.0)	2.5 (2.0-4.0)	-
Mode of surgery, n (%)						
Open	26* (31)	19* (33)	7 (27)	18* (36)	6 (27)	2 (18)
Laparoscopic	57 (69)	38 (67)	19 (73)	32 (64)	16 (73)	9 (82)
Pathological local tumour stage, n (%)						
pT2c	16 (64)	14 (78)	2 (29)	13 (76)	2 (33)	1 (50)
pT3a	7 (28)	4 (22)	3 (43)	4 (34)	2 (33)	1 (50)
pT3b	2 (8)	-	2 (29)	-	2 (33)	-

PSA = prostate specific antigen; N0 = no lymph node metastases, neither in the sentinel nodes nor in the ePLND specimens; N1 = lymph node metastases detected either by sentinel node analysis or by ePLND; SN0 = no metastases detected in the SNs; SN1 = metastases detected in the SNs; SNx = no sentinel nodes were detected; SD = standard deviation; IQR = inter-quartile range

* In one patient who underwent open surgery it was not possible to perform the prostatectomy due to anatomical difficulties.

Table 2. Locations of the sentinel lymph nodes detected outside the template of an extended pelvic lymph node dissection, and locations of the metastases found in those lymph nodes.

	No. of sentinel nodes	No of sentinel nodes with. metastases
Lateral to the external iliac artery	5	1
Medial to the umbilical ligament	1	1
Medial to the internal iliac artery	9	5
At the common iliac artery above the ureteral crossing	5	0

Table 3. Performance of sentinel node and extended pelvic lymph node dissection (ePLND) (a) for the 72 patients where at least one sentinel node was detected, (b) for all the 83 patients, where an inconclusive SN detection is defined as negative.

a)

	Sentinel node		ePLND	
	Negative	Positive	Negative	Positive
N0	49	0	49	0
N1	1	22	2	21
Sensitivity	0.96 (0.76-1.0)		0.91 (0.70-0.98)	
Specificity	1.0 (0.91-1.0)		1.0 (0.91-1.0)	
NPV	0.98 (0.88-1.0)		0.96 (0.85-0.99)	
PPV	1.0 (0.82-1.0)		1.0 (0.81-1.0)	

b)

	Sentinel node		ePLND	
	Negative	Positive	Negative	Positive
N0	57	0	57	0
N1	4	22	2	24
Sensitivity	0.85 (0.64-0.95)		0.92 (0.73-0.99)	
Specificity	1.0 (0.92-1.0)		1.0 (0.92-1.0)	
NPV	0.93 (0.83-0.98)		0.97 (0.87-0.99)	
PPV	1.0 (0.82-1.0)		1.0 (0.83-1.0)	

Values within brackets are 95% confidence intervals. N0 = node negative, defined as negative by both methods; N1= node positive, defined as positive by either method; ePLND = extended pelvic lymph node dissection; NPV = negative predictive value; PPV = positive predictive value.