Pelvic Lymph Node Metastases in Prostate Cancer: Preoperative Detection With Dynamic Contrast-Enhanced Magnetic Resonance Imaging Compared With Postoperative Pathologic Result of Pelvic Lymph Node Dissection

Hoyoung Ryu¹, Byeongdo Song², Jinho Hwang², Sung Kyu Hong²,
Seok-Soo Byun², Sang Eun Lee², Sangchul Lee²

¹Department of Urology, Seoul National University Hospital, Seoul, Korea

²Department of Urology, Seoul National University Bundang Hospital, Seongnam, Korea

Purpose: The aim of this study is evaluating the accuracy of preoperative magnetic resonance imaging (MRI) in patients who underwent pelvic lymph node dissection (PLND).

Materials and Methods: The medical records of 1,528 patients who underwent radical prostatectomy and PLND from 2003 to 2017 in Seoul National University Bundang Hospital were retrospectively reviewed. We evaluated the various clinicopathologic variables including preoperative MRI findings and pathologic lymph node (LN) metastasis. The prediction model for pathologic LN metastasis was assessed using univariate and multivariable logistic regression analyses and areas under receiver operating characteristic (ROC) curves.

Results: The mean age of our cohort was 66.4±6.7 years. Positive LN finding of preoperative MRI finding was observed in 9.4% (145 of 1,528) of patients. 5.3% (81 of 1,528) of patients had confirmed final pathologic LN metastases. Sensitivity and specificity of preoperative MRI were 30.8% and 91.7%, respectively. Multivariable analysis showed that preoperative MRI findings, clinical stage and biopsy Gleason score were independent significant predictors for pathologic LN metastasis ($p < 0.001$, $p = 0.002$, and $p < 0.001$, respectively). Prediction model using preoperative MRI findings and National Comprehensive Control Network risk stratification showed fair accuracy using ROC analysis.

Conclusions: Preoperative MRI findings for pathologic LN metastasis showed limited prediction value. A large-scale, multicenter, prospective study is needed to fully evaluate the clinical significance of preoperative MRI. (Korean J Urol Oncol 2017;15:158-164)

Key Words: Prostate • Radical prostatectomy • Magnetic resonance imaging • Lymph nodes

Received October 20, 2017, Revised October 23, 2017,
Accepted October 23, 2017

Corresponding Author: Byeongdo Song

Department of Urology, Seoul National University Bundang Hospital,
82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
E-mail: uromedi@naver.com

Tel: +82-31-787-7345, Fax: +82-31-787-4057

ORCID code: <https://orcid.org/0000-0003-3961-1258>

• This research was supported by a grant of the Korean Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI17C1264).

INTRODUCTION

Prostate cancer is the most common cancer in men and the third most common cause of death among malignancies in male population.¹ For localized prostate cancer, definite treatments such as radical prostatectomy (RP) or radiation therapy could be primary therapeutic options. However, once prostate cancer invades lymph node or other organs, therapeutic effects of such

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

2017 © Copyright The Korean Urological Oncology Society and The Korean Prostate Society. All Rights Reserved.

treatment modalities become limited. Even if the therapeutic role of pelvic lymph node dissection (PLND) in patients with low-risk prostate cancer is still an open question, patients with intermediate- to high-risk disease are likely to benefit from PLND.² For this reason, early detection of lymph node invasion (LNI) is important for treatment of prostate cancer.

The Partin tables,³ the National Comprehensive Control Network (NCCN) practice guidelines nomogram,^{4,5} the D'Amico risk-classification^{6,7} are commonly used to assess the risk of prostate cancer. Such risk assessment tools use preoperative variables including prostate-specific antigen (PSA), biopsy Gleason score, and clinical stage to predict prognosis of LNI and prostate cancer after treatments.

However, such preoperative assessing tools do not include preoperative image studies including magnetic resonance imaging (MRI). Recently, the multiparacentric MRI (mp-MRI), which is the combination of conventional T1-weighted MRI (T1WI) and T2-weighted MRI (T2WI) with various functional imaging modalities including diffusion-weighted MRI (DWI), dynamic contrast enhanced MRI (DCEI), and magnetic resonance spectroscopy, has been applied in clinical field.⁸ The role of mp-MRI has been expanded broadly to prostate biopsy, active surveillance, advanced disease detection, and local recurrence detection after RP.⁹ However, the diagnostic value of imaging studies including MRI are still debatable. Wolf et al.¹⁰ reported that CT and MRI showed high specificity of 97%, but relatively low sensitivity of 36%. They concluded that nodal imaging studies should only be recommended for patients having a probability of 45% or higher for LNI. Min et al.¹¹ reported that a combined approach of T1W, T2W, and DCEI with DWI demonstrated an accurate detection rate of prostate cancer, showing high specificity but relatively lower sensitivity. Hövels et al.¹² reported MRI demonstrated an equally poor performance in the detection of LNIs from prostate cancer through meta-analysis.

The aim of this study is demonstrating the predictive power of preoperative MRI for LNI in prostate cancer patients who underwent PLND.

MATERIALS AND METHODS

With an approval from Institutional Review Board (B-1710-427-110), the medical records of 3,379 patients who underwent RP for prostate cancer at Seoul National University

Bundang Hospital from November 2003 to May 2017 were analyzed retrospectively. After excluding patients who did not undergo PLND and those with missing data about lymph node state, 1,528 patients were included in our analyses. We evaluated the various clinicopathologic variables including preoperative MRI and pathologic LNI.

In our institution, every patient diagnosed with prostate cancer underwent preoperative prostate MRI, including T1WI, T2WI, DWI, and DCEI. Positive lymph node enlargement (LNE) on MRI was defined when increased over 10 mm.

We stratified the cohorts into 3 groups according to the number of LNE: no significant LNE group, one LNE group, and more than 2 LNE group. Each group was graded as 0, 1, and 2, respectively.

Along with preoperative MRI, we used the NCCN risk stratification to predict diagnostic values for metastasis. In NCCN risk stratification system, there are 5 risk categories: very low (T1c and Gleason score ≤ 6 and PSA < 10 ng/mL and < 3 positive core biopsies); low (T1-T2a and Gleason score ≤ 6 and PSA < 10 ng/mL); intermediate (T2b-T2c or Gleason score 7 or PSA = 10–20 ng/mL); high (T3a or Gleason score 8–10 or PSA > 20 ng/mL); and very high (T3b-T4 or Gleason primary pattern 5).¹³ The entire cohorts were classified into 3 categories as followings: low-risk group (very low-risk and low-risk group), intermediate-risk group, and high-risk group (high-risk and very high-risk group) according to NCCN risk stratification, with each group graded as 0, 1, 2, respectively. To assess predictive power of combination of preoperative MRI and NCCN risk stratification, we added the numerical grades of MRI group (0, 1, and 2) and NCCN risk group (0, 1, and 2).

The prediction model for pathologic lymph node metastasis was evaluated using univariate and multivariable logistic regression analyses. Areas under receiver operating characteristic (ROC) curves (AUC) was used as an index of diagnostic accuracy.

IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis, and ROC curve and the prediction factors were estimated using MEDCALC ver. 12 (MedCalc, Ostend, Belgium). All p-values were 2-sided, and $p < 0.05$ was considered as a significant result.

RESULTS

Demographic characteristics of subjects were as shown in

Table 1. The mean age of the cohort was 66.4 ± 6.7 years. Median concentration of serum PSA was 11.34 ng/dL (interquartile range, 6.91–20.11 ng/dL). Positive preoperative MRI finding was observed in 9.4% (145 of 1,528) of patients. 5.3% (81 of 1,528) of patients had confirmed final pathologic lymph node metastases.

Multivariable analysis showed that preoperative MRI findings ($p < 0.001$), clinical stage ($p = 0.001$) and biopsy Gleason score ≥ 8 ($p < 0.001$) were significant independent predictors for

Table 1. Baseline characteristics of patients (n=1,528)

Characteristic	Value
Age (yr)	66.4 ± 6.7 (41–82)
BMI (kg/m^2)	24.5 ± 2.8 (14.2–54.9)
PSA (ng/dL)	11.3 (6.9–20.1)
Volume of prostate (g)	35.8 ± 14.2 (9.3–116.0)
Gleason biopsy grade	
6	299 (19.6)
7	752 (49.2)
$8 \geq$	477 (31.2)
Clinical stage	
T1c	773 (50.6)
T2a	415 (27.2)
T2b+T2c	54 (3.5)
$> T3$	286 (18.7)
Risk group	
Low	156 (10.2)
Intermediate	617 (40.4)
High	755 (49.4)
Operation method	
RALP	1,060 (69.4)
RRP	458 (30.0)
LRP	10 (0.6)
MRI LN positivity	145/1,528 (9.4)
1	126
2	19
Mean PLND LN yield	7.7 ± 5.5 (1–34)
PLND LN positivity	81/1,528 (5.3)
1	43
2	22
3	11
4	3
5	1
6	1

Values are presented as mean $\pm$ standard deviation (range), median (interquartile range), number (%), or number.

BMI: body mass index, PSA: prostate specific antigen, RALP: robot-assisted laparoscopic radical prostatectomy, RRP: radical retropubic prostatectomy, LRP: laparoscopic radical prostatectomy, MRI: magnetic resonance imaging, LN: lymph node, PLND: pelvic lymph node dissection.

pathologic LN metastasis (Table 2).

Preoperative mp-MRI (T1W, T2W, DWI, and DCEI) of prostate alone achieved a sensitivity of 30.86% and a specificity of 91.71%, respectively. NCCN risk alone and the combination of preoperative mp-MRI and NCCN risk stratification achieved sensitivities of 90.12% and 99.45% respectively, and specificities of 52.87% and 49.38% respectively (Table 3).

Among 145 patients with positive LN on preoperative MRI, only 25 patients had confirmed final pathologic lymph node metastases. Especially, Among 126 patients with one positive LN on preoperative MRI, only 21 patients (16.7%) had confirmed final pathologic lymph node metastasis (Table 4).

Through ROC analysis, prediction model using preoperative MRI findings alone showed AUC value of 0.613 (0.588–0.638). The addition of preoperative MRI findings to NCCN risk stratification showed fair accuracy, improving the AUC to 0.758 (0.735–0.779) from 0.613 with NCCN risk stratification alone (Fig. 1).

DISCUSSION

There are several pretreatment prostate cancer risk stratification systems or nomograms based on prognostic power of initial PSA, biopsy Gleason score and clinical T stage including D'Amico risk stratification, NCCN practice guideline risk-stratification, and the D'Amico risk-classification.¹⁴

The Partin tables are the first nomogram to predict rates of organ-confined disease, positive margins, the risk of seminal vesicle and lymph node positivity after RP, which uses commonly available preoperative factors including serum PSA level, clinical stage and biopsy Gleason score.¹⁵ The Partin tables were initially established based on the information of the patients who underwent RP between 1982 and 1991, and it was upgraded with newer data acquired between 2006 to 2011.¹⁶ The predictive accuracy of the Partin tables for LNI was from 76% to 84%.^{17–20} Recently, the Partin tables are commonly used for making therapeutic decision to perform a lymphadenectomy at the time of RP. The NCCN guideline risk stratification contains the minimum of clinical stage, grade and PSA it is applied for the selection of optimal therapeutic options as well as for the prediction of biochemical failure rate after definitive local therapy.^{4,21} NCCN practice guideline LNI nomogram is also used for predicting the prognosis of LN positive disease after lymphadenectomy. Moreover, the D'Amico risk-classification

Table 2. Univariate and multivariable competing risks analysis evaluating of lymph node invasion and risk factors

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.003	0.970–1.037	0.882	-	-	-
Body mass index	0.962	0.886–1.043	0.347	-	-	-
Smoking amount (pack×year)	0.997	0.984–1.010	0.625	-	-	-
Operation methods						
Open vs. robotic	0.697	0.412–1.179	0.179	-	-	-
Prostate volume on TRUS	1.010	0.996–1.024	0.179	-	-	-
NCCN risk group	7.639	3.881–15.033	<0.001			
Low vs. intermediate	1.779	0.217–14.564	0.591	-	-	-
Low vs. high	16.591	2.288–120.288	0.005	-	-	-
PSA	1.014	1.008–1.020	<0.001	-	-	-
Clinical stage						
Stage T1c	-	-	-	-	-	-
Stage T2	2.737	1.599–4.687	<0.001	2.516	1.448–4.370	0.001
Stage ≥T3	7.661	4.160–14.107	<0.001	2.853	2.853–10.308	<0.001
Gleason score						
6	-	-	-	-	-	-
7	3.596	0.782–16.531	0.101	3.843	0.828–17.832	0.085
≥8	13.998	3.410–57.467	<0.001	11.683	2.812–48.541	0.001
DRE	2.798	1.782–4.391	<0.001			
MRI LNI positive	3.375	2.266–5.027	<0.001	2.694	1.707–4.251	<0.001

HR: hazard ratio, CI: confidence interval, TRUS: transrectal ultrasound, NCCN: National Comprehensive Control Network, PSA: prostate-specific antigen, DRE: digital rectal examination, MRI: magnetic resonance imaging, LNI: lymph node invasion.

Table 3. Sensitivity, specificity, and predictive values of each risk stratifications

Variable	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)
Preoperative MRI	30.86	91.71	17.24	95.95	0.613 (0.543–0.684)
NCCN	90.12	52.87	9.67	98.97	0.717 (0.671–0.763)
Preoperative MRI + NCCN	99.45	49.38	33.33	94.92	0.758 (0.707–0.809)

PPV: positive predictive value, NPV: negative predictive value, AUC: areas under receiver operating characteristic curves, CI: confidence interval, MRI: magnetic resonance imaging, NCCN: National Comprehensive Control Network.

was originally developed to predict biochemical recurrence in prostate cancer patients after treatment.⁶

These 3 tools have been applied frequently in routine clinical practice. When comparing these 3 tools for prediction of LNI, Abdollah et al.²⁰ showed that NCCN guideline LNI nomogram (AUC 82%) outperformed the Partin tables (73%) and the D'Amico risk-classification (75%).

However, among these 3 nomograms, imaging studies including preoperative MRI has not been accepted as essential parameter to predict LNI. Therefore, we investigated whether preoperative MRI could improve predictive power of conventional nomograms. This study aimed to evaluate the accuracy of preoperative MRI in patients who underwent RP with PLND

and determinate whether preoperative MRI could improve the diagnostic value of conventional NCCN.

The advent of mp-MRI is known to provide more accurate mean of diagnosing prostate cancer in men with elevated PSA level, achieving a specificity of 90%, a negative predictive value of 85%.^{22,23} To achieve the highest sensitivity and specificity in detecting and assessing suspicious lesion within prostate, mp-MRI combines conventional T1WI and T2WI with various functional imaging modalities, with a minimum of 2 modalities. DWI and magnetic resonance spectroscopic imaging add specificity for lesion characterization, and DCE adds sensitivity for cancer detection.⁸

There are several guidelines from the European Association

Table 4. Final lymph node pathology of patients who have positive lymph node findings on preoperative MRI

Positive LN on preoperative MRI	MRI LN=1	MRI LN≥2
Negative pathologic LNI	105 (83.3)	15 (78.9)
Positive pathologic LNI	21 (16.7)	4 (21.1)
Pathologic LNI		
0	105 (83.3)	15 (78.9)
1	8 (6.3)	0 (0)
2	7 (5.6)	2 (10.5)
3	3 (2.4)	2 (10.5)
4	2 (1.6)	0 (0)
5	0 (0)	0 (0)
6	1 (0.8)	0 (0)

Values are presented as number (%).

MRI: magnetic resonance imaging, LN: lymph node, LNI: lymph node invasion.

of Urology (EAU), the American Urological Association (AUA), and the NCCN, mentioning the potential role of mp-MRI in prostate biopsy, active surveillance, and recurrent prostate cancer.⁹

The EAU guideline suggests that mp-MRI followed by transrectal ultrasonography (TRUS)-guided or MRI-guided biopsies might be useful to detect prostate cancer especially in anterior region, whereas conventional TRUS-guided biopsy is still performed more frequently instead of the corresponding newer modalities. However, mp-MRI is not recommended for the purpose of staging in case of low-risk prostate cancer, except when the results of MRI could influence management.²⁴ The AUA guideline suggests that mp-MRI could identify local recurrence lesion and improve salvage radiation targeting,²⁵ and the NCCN guideline suggests that mp-MRI could aid in deciding active surveillance, yet concluded mp-MRI is not recommended for routine use.²⁶

In detecting lymph node metastasis, mp-MRI showed a high specificity of 91%–97% but a low sensitivity of 14%–36%.^{10,11,27} Hövels et al.¹² mentioned poor performance of MRI in detection of lymph node metastasis through meta-analysis study. Because of such low sensitivity, mp-MRI alone was not recommended for lymph node workup in patients without suspicious lymph node lesions on CT.²⁸ To evaluate predictive power of preoperative MRI for LNI, we analyzed the medical records of 1,528 patients who underwent RP with PLND, which is the largest cohort as far as we know.

In this study, the mp-MRI showed a high specificity of 91.7% and relatively a low sensitivity of 30.8%, which are sim-

Fig. 1. Receiver operating characteristic curves: prediction model using preoperative MRI findings and NCCN risk stratification. MRI: magnetic resonance imaging, NCCN: National Comprehensive Control Network.

ilar to the previous study results. The ROC curve of preoperative MRI alone showed AUCs of 0.613 for lymph node metastasis. ROC curve of NCCN nomogram showed AUCs of 0.713 that was similar to the results of Abdollah et al.²⁰

When combining risk grades of NCCN nomogram with the outcomes of preoperative MRI, the specificity and the sensitivity were 99.5% and 49.4%, respectively. The ROC curve showed AUCs of 0.782. When the corresponding 2 parameters were combined, the AUCs became smaller than 0.9, but the value was greater compared to 0.613 and 0.713 of single parameters.

There are several limitations in this study. At first, while the large number of cohort enabled us to detect significant differences, our database is derived from the retrospective records of patients who were treated at single institution. Therefore, multi-institutional studies might be needed to confirm our findings. Furthermore, we were unable to match and compare the locations of lymph node lesions shown in preoperative MRI with the actual pathologically confirmed LNI sites. Moreover, the lack of information on long-term survival including cancer-specific survival or overall survival could be another limitation to our study.

CONCLUSIONS

Our results show that preoperative MRI findings for pathologic LN metastasis alone showed limited prediction value. However, when combining with conventional NCCN risk

nomogram, preoperative MRI could improve predictive power. A large-scale, multicenter, and prospective study is needed to fully evaluate the clinical significance of preoperative MRI.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017;67:7-30.
2. Joung JY, Cho IC, Lee KH. Role of pelvic lymph node dissection in prostate cancer treatment. *Korean J Urol* 2011;52: 437-45.
3. Makarov DV, Trock BJ, Humphreys EB, Mangold LA, Walsh PC, Epstein JI, et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. *Urology* 2007;69:1095-101.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Prostate Cancer Version 3 [Internet]. Fort Wathington (PA): National Comprehensive Cancer Network; 2016 [cited on 2017 Jan 2]. Available from: <https://www.tri-kobe.org/nccn/guideline/urological/english/prostate.pdf>.
5. Cagiannos I, Karakiewicz P, Eastham JA, Ohori M, Rabbani F, Gerigk C, et al. A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. *J Urol* 2003;170:1798-803.
6. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969-74.
7. Boorjian SA, Karnes RJ, Rangel LJ, Bergstralh EJ, Blute ML. Mayo Clinic validation of the D'Amico risk group classification for predicting survival following radical prostatectomy. *J Urol* 2008;179:1354-60.
8. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. *Eur Radiol* 2012;22:746-57.
9. Yoo S, Kim JK, Jeong IG. Multiparametric magnetic resonance imaging for prostate cancer: a review and update for urologists. *Korean J Urol* 2015;56:487-97.
10. Wolf JS Jr, Cher M, Dall'era M, Presti JC Jr, Hricak H, Carroll PR. The use and accuracy of cross-sectional imaging and fine needle aspiration cytology for detection of pelvic lymph node metastases before radical prostatectomy. *J Urol* 1995;153(3 Pt 2):993-9.
11. Min BD, Kim WT, Cho BS, Kim YJ, Yun SJ, Lee SC, et al. Usefulness of a combined approach of T1-weighted, T2-weighted, dynamic contrast-enhanced, and diffusion-weighted imaging in prostate cancer. *Korean J Urol* 2012;53:830-5.
12. Hövels AM, Heesakkers RA, Adang EM, Jager GJ, Strum S, Hoogeveen YL, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. *Clin Radiol* 2008;63:387-95.
13. Mohler JL, Armstrong AJ, Bahnson RR, D'Amico AV, Davis BJ, Eastham JA, et al. Prostate cancer, version 1.2016. *J Natl Compr Canc Netw* 2016;14:19-30.
14. Rodrigues G, Warde P, Pickles T, Crook J, Brundage M, Souhami L, et al. Pre-treatment risk stratification of prostate cancer patients: a critical review. *Can Urol Assoc J* 2012;6: 121-7.
15. Partin AW, Kattan MW, Subong EN, Walsh PC, Wojno KJ, Oesterling JE, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. *JAMA* 1997;277:1445-51.
16. Eifler JB, Feng Z, Lin BM, Partin MT, Humphreys EB, Han M, et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. *BJU Int* 2013;111:22-9.
17. Blute ML, Bergstralh EJ, Partin AW, Walsh PC, Kattan MW, Scardino PT, et al. Validation of Partin tables for predicting pathological stage of clinically localized prostate cancer. *J Urol* 2000;164:1591-5.
18. Yu JB, Makarov DV, Sharma R, Peschel RE, Partin AW, Gross CP. Validation of the partin nomogram for prostate cancer in a national sample. *J Urol* 2010;183:105-11.
19. Penson DF, Grossfeld GD, Li YP, Henning JM, Lubeck DP, Carroll PR. How well does the Partin nomogram predict pathological stage after radical prostatectomy in a community based population? Results of the cancer of the prostate strategic urological research endeavor. *J Urol* 2002;167:1653-7.
20. Abdollah F, Schmitges J, Sun M, Thuret R, Djahangirian O, Tian Z, et al. Head-to-head comparison of three commonly used preoperative tools for prediction of lymph node invasion at radical prostatectomy. *Urology* 2011;78:1363-7.
21. D'Amico AV, Whittington R, Malkowicz SB, Fondurulia J, Chen MH, Kaplan I, et al. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. *J Clin Oncol* 1999;17:168-72.
22. Thompson J, Lawrentschuk N, Frydenberg M, Thompson L, Stricker P; USANZ. The role of magnetic resonance imaging in the diagnosis and management of prostate cancer. *BJU Int* 2013;112 Suppl 2:6-20.
23. Raz O, Haider M, Trachtenberg J, Leibovici D, Lawrentschuk N. MRI for men undergoing active surveillance or with rising PSA and negative biopsies. *Nat Rev Urol* 2010;7:543-51.
24. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S,

- van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol* 2014;65:467-79.
25. Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, Hahn C, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. *J Urol* 2013;190:441-9.
26. Mohler JL, Kantoff PW, Armstrong AJ, Bahnson RR, Cohen M, D'Amico AV, et al. Prostate cancer, version 2.2014. *J Natl Compr Canc Netw* 2014;12:686-718.
27. Jeong IG, Lim JH, You D, Kim MH, Choi HJ, Kim JK, et al. Incremental value of magnetic resonance imaging for clinically high risk prostate cancer in 922 radical prostatectomies. *J Urol* 2013;190:2054-60.
28. Van den Bergh L, Lerut E, Haustermans K, Deroose CM, Oyen R, Isebaert S, et al. Final analysis of a prospective trial on functional imaging for nodal staging in patients with prostate cancer at high risk for lymph node involvement. *Urol Oncol* 2015;33:109.e23-31.