Is pelvic lymph node dissection necessary in patients with biopsy proven Gleason 6 prostate cancer? – analysis of the SEER database

Michael Daugherty, MD, Dillon Sedaghatpour, MD, Gennady Bratslavsky, MD, Oleg Shapiro, MD

Department of Urology, SUNY Upstate Medical University, Syracuse, New York, USA

DAUGHERTY M, SEDAGHATPOUR D, BRATSLAVSKY G, SHAPIRO O. Is pelvic lymph node dissection necessary in patients with biopsy proven Gleason 6 prostate cancer? – analysis of the SEER database. *Can J Urol* 2018;25(4):9414-9420.

Introduction: *Since the advent of prostate-specific antigen (PSA) screening there has been a decreased incidence of lymph node positive disease (LND). Nevertheless, because of possible upgrading, LND is frequently performed with preoperative Gleason 6 prostate cancer. We utilized the Surveillance Epidemiology and End Results (SEER) database to evaluate the frequency of LND and preoperative variables for node positivity in contemporary patients with preoperative Gleason 6 disease.*

Materials and methods: *SEER-18 registries database was queried for all patients diagnosed with prostate cancer between the years 2010 and 2014. Patients were excluded that had unknown histology or unknown preoperative or postoperative Gleason score. We evaluated the rate of LND, Gleason upgrading, and node positive events.*

Results: *There were 16,544 patients with preoperative Gleason 6 disease that met our inclusion criteria. Of these, 35.4% (5,856 patients) had LND and 64.6% (10,688 patients) did not. Gleason upgrade on final pathology was found in 51.9% and 45.0% of the LND and no LND cohorts, respectively. There were only 62 (1.1%) patients with node positive disease following LND. These patients had higher preoperative PSA and clinical stage disease.*

Conclusion: *In a contemporary cohort of patients with preoperative Gleason 6 prostate cancer LND continues to be performed in about 35% of cases. Despite significant rate of Gleason upgrading on final pathology, only 1% will have node positive disease. With available data on morbidity of LND, the LND for preoperative Gleason 6 prostate in contemporary PSA screened cancer cohorts is likely not warranted.*

Key Words: prostate cancer, lymph node dissection, Gleason 6

Introduction

Prostate cancer is the most frequently diagnosed cancer in men in the United States.[1] With the advent of prostate-specific antigen (PSA) screening, the incidence of prostate cancer has dramatically increased in the past three decades[1] until recent USPTF recommendations.[2] Earlier detection has led to earlier diagnosis of lower stage prostate cancer with an estimated 161,360 new cases diagnosed in 2017 compared to 66,000 in 1980.[3,4]

Gleason score (GS) of prostate biopsy specimens remains an independent variable responsible for prognosis and decision making strategies for million patients.[5] Gleason 6 prostate cancers have been shown to have low metastatic potential and portend favorable

Accepted for publication May 2018

Address correspondence to Dr. Oleg Shapiro, Department of Urology, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210 USA

prognosis, with several studies demonstrating that men with GS 6 disease have less than a 1% chance of lymph node invasion (LNI).[6-9] Well known Partin tables estimate lymph node (LN) involvement to be less than 2% for any PSA or clinical stage for patients with GS 6 on prostate biopsy.[10] In addition, a recent study by Ross et al showed that among 14,123 patients with a final GS 6, there were no patients with LN positive disease.[8] Nevertheless, it remains impossible to know which preoperative GS 6 patients would be upgraded on the final pathology, likely explaining why many patients treated with surgery for preoperative Gleason 6 prostate cancer still undergo a pelvic lymph node dissection (LND).[7,11]

Utilizing Surveillance Epidemiology and End Results (SEER) database we aimed to identify the rate of LND being performed in contemporary patients with preoperative GS 6 prostate cancer, identify LN positivity rates, and identify variables for having LN positive disease on final pathology.

Materials and methods

The SEER-18 registries database was queried for all patients diagnosed with biopsy proven Gleason 6 prostate cancer between the years 2010 and 2014 that underwent a prostatectomy (site specific surgery codes 50, 70 and 80). These years were included, as penetration of extended prostate biopsy scheme has become prevalent and adapted in most US centers. Information on number of biopsy cores taken and number of cores positive were also available for patients diagnosed from the year 2010 and later. There was no information regarding percentage of the positive cores involved with cancer. Patients with unknown histology, unknown preoperative and postoperative GS, unknown number of biopsy cores examined, unknown PSA level, and unknown LND status were excluded from the analysis. Patients were analyzed as one cohort and then were subdivided into groups that underwent LND and those that did not. The rate of Gleason upgrading was compared in those that had LND with those who did not.

The following variables were analyzed: patients' age, race, PSA, clinical T stage, pathologic T stage, total number of biopsy cores and number of cores positive, postoperative GS, number of LN removed (if performed), and pathologic nodal status. T-tests were used to compare continuous variables and Chi-square analysis was used to compare patient and tumor characteristics in those that had LND with those who did not. Statistical significance was set at p value ≤ 0.05 for all variables. STATA 14.1 (STATA Corp. College Station, TX, USA) software was used to perform statistical analysis.

Results

A total of 32,229 patients with GS 6 cancer on prostate biopsy were identified that subsequently underwent radical prostatectomy. After applying our inclusion criteria, 16,544 patients were available for analysis. A total of 5,856 (35.4%) patients had 1 or more lymph nodes removed at time of prostatectomy whereas 10,688 (64.6%) patients had no lymph nodes removed at time of prostatectomy, Table 1. On final pathology, 7,852 (47.5%) patients had an upgraded GS, Table 2. Those patients with Gleason upgrading had more clinical T3 staging preoperatively (1.7% versus 1.4% versus 0.39%). For those patients that underwent Gleason upgrading on final pathology, the majority of patients had ISUP Grade Group 2, Figure 1.

Of the 5,856 patients with LND, 62 (1.1%) had a pathologically confirmed LN disease. There were 8 patients with node positive disease that had GS 6 disease on final pathology. A larger proportion of patients with node positive disease were of black race (27.4% versus 12.4%, p < 0.0001). Patients with node positive disease had a higher clinical stage preoperatively, a higher PSA level, and a higher percent of biopsy cores positive for cancer (p < 0.0001 for all comparisons).

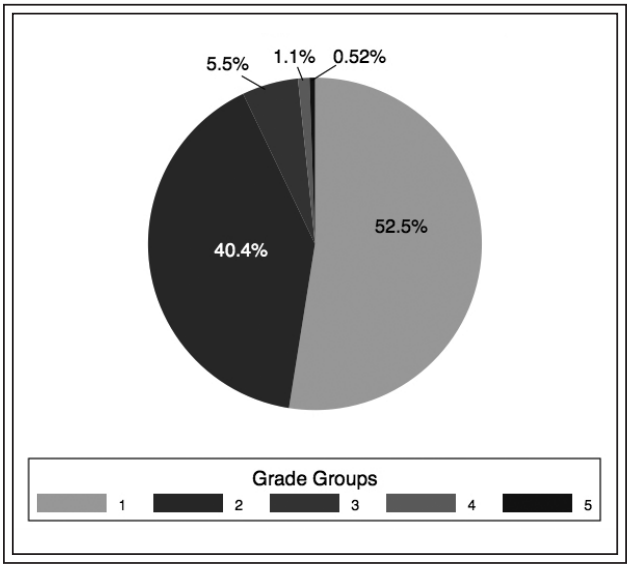

Figure 1. ISUP Grade groups on final pathology specimen for those patients with complete information (n = 16,511).

TABLE 1. **Patient demographics, tumor characteristics, and prostate biopsy information for all patients, stratified by lymph node dissection and nodal status**

	All patients (n = 16,544)	LND (n = 5,856)	No LND (n = 10,688)	p value[a]	Node negative (n = 5,792)	Node positive (n = 62)	p value[b]
Age				0.0001			0.10
Mean	59.72	60.0	59.6		60.0	61.5	
Median	60.0	60.0	60.0		60.0	61.0	
Age groups				0.023			0.28
< 50	7.7%	7.2%	8.0%		7.3%	3.2%	
51-54	15.8%	15.1%	16.2%		15.1%	12.9%	
55-59	24.7%	24.3%	24.9%		24.3%	27.4%	
60-64	24.7%	24.8%	24.6%		24.8%	17.7%	
65-69	20.2%	21.2%	19.6%		21.1%	25.8%	
≥ 70	7.0%	7.4%	6.7%		7.4%	12.9%	
Race				0.28			0.001
White	81.6%	81.4%	81.7%		81.6%	66.1%	
Black	12.8%	12.6%	12.9%		12.4%	27.4%	
Other	4.7%	4.9%	4.6%		5.0%	3.2%	
Unknown	0.9%	1.1%	0.81%		1.0%	3.2%	
PSA				< 0.0001			< 0.0001
Mean	6.7	7.8	6.1		7.7	16.0	
Median	5.3	5.6	5.2		5.6	10.6	
Clinical T stage				< 0.0001			< 0.0001
T1a/b	0.45%	0.44%	0.45%		0.45%	0.0%	
T1c	73.9%	70.6%	75.7%		70.7%	64.5%	
T2	15.8%	18.6%	14.2%		18.6%	19.4%	
T3	0.88%	1.3%	0.67%		1.2%	11.3%	
Localized, NOS	9.0%	9.0%	9.0%		9.1%	4.8%	
Pathologic T stage				< 0.0001			< 0.0001
T1	0.27%	0.19%	0.31%		0.19%	0.0%	
T2	87.7%	84.4%	89.41%		85.0%	29.0%	
T3	12.0%	15.2%	10.2%		14.7%	69.4%	
T4	0.13%	0.15%	0.11%		0.14%	1.6%	
Prostatectomy Gleason score				< 0.0001			< 0.0001
< Gleason 6	0.57%	0.68%	0.51%		0.69%	0.0%	
Gleason 6	52.0%	47.4%	54.5%		47.8%	12.9%	
Gleason 7	45.8%	49.8%	43.7%		49.6%	71.0%	
Gleason 8	1.1%	1.4%	0.96%		1.3%	11.3%	
Gleason 9	0.5%	0.72%	0.37%		0.67%	4.8%	
Gleason 10	0.02%	0.02%	0.03%		0.02%	0.0%	
Cores taken				0.03			0.007
Mean	12.15	12.25	12.1		12.2	13.9	
Median	12	12	12		12.0	12.0	
Cores positive				< 0.0001			< 0.0001
Mean	3.42	3.8	3.2		3.8	5.7	
Median	3	3	2		3	5	
Percent positive				< 0.0001			< 0.0001
Mean	30.8%	33.7%	29.3%		33.6%	47.7%	
Median	25.0%	25.0%	23.1%		25.0%	43.6%	

[a]lymph node dissection versus no lymph node dissection; [b]node negative versus node positive

TABLE 2. **Patient demographics, tumor characteristics, and prostate biopsy information for patients with Gleason upgrading on final pathology, stratified by lymph node dissection status.**

	Gleason upgrade (n = 7,852)	No Gleason upgrade (n = 8,692)	p value[a]	LND & GS upgrade (n = 3,040)	No LND & GS upgrade (n = 4,812)	p value[b]
Age			< 0.0001			0.81
Mean	60.4	59.1		60.4	60.4	
Median	61.0	59.0		61	61	
Age groups			< 0.0001			0.52
< 50	6.5%	8.8%		6.5%	6.5%	
51-54	14.1%	17.4%		13.8%	14.3%	
55-59	23.3%	25.9%		23.8%	23.0%	
60-64	25.5%	23.9%		24.8%	25.9%	
65-69	22.3%	18.2%		23.2%	21.8%	
≥ 70	8.3%	5.74%		7.9%	8.5%	
Race			0.0007			0.007
White	80.5%	82.5%		79.5%	81.2%	
Black	13.6%	12.1%		13.6%	13.6%	
Other	5.0%	4.4%		5.8%	4.6%	
Unknown	0.87%	0.93%		1.2%	0.67%	
PSA			< 0.0001			< 0.0001
Mean	7.3	6.2		8.7	6.5	
Median	5.6	5.1		6.0	5.5	
Clinical T stage			< 0.0001			< 0.0001
T1a/b	0.36%	0.53%		0.40%	0.33%	
T1c	72.8%	74.9%		69.9%	74.6%	
T2	16.0%	15.6%		19.2%	14.0%	
T3	1.4%	0.39%		1.8%	1.2%	
Localized, NOS	9.4%	8.7%		8.7%	9.9%	
Pathologic T stage			< 0.0001			< 0.0001
T1	0.2%	0.32%		0.23%	0.19%	
T2	79.9%	94.7%		75.2%	82.8%	
T3	19.7%	5.0%		24.3%	16.9%	
T4	0.2%	0.06%		0.26%	0.17%	
Cores taken			0.01			0.06
Mean	12.0	12.2		12.2	12.0	
Median	12.0	12.0		12.0	12.0	
Cores positive			< 0.0001			< 0.0001
Mean	3.8	3.0		4.3	3.5	
Median	3.0	2.0		4.0	3.0	
Percent positive			<0.0001			<0.0001
Mean	34.5%	27.5%		38.0%	32.3%	
Median	28.6%	18.8%		33.3%	25.0%	

[a]GS upgrade vs. no GS upgrade [b]LND & GS upgrade vs. no LND & GS upgrade

The mean and median number of lymph nodes removed was 6.23 and 4, respectively. The majority of patients had 1-5 lymph nodes removed during surgery, Figure 2. Patients with LND were slightly older than those without LND (60.0 years versus 59.6 years, p = 0.0001), however there was no difference in race between groups (p = 0.28). Patients with LND also presented with higher clinical stage disease than those who did not undergo LND (p < 0.0001). However, the vast majority of all patients were presenting with T1 disease.

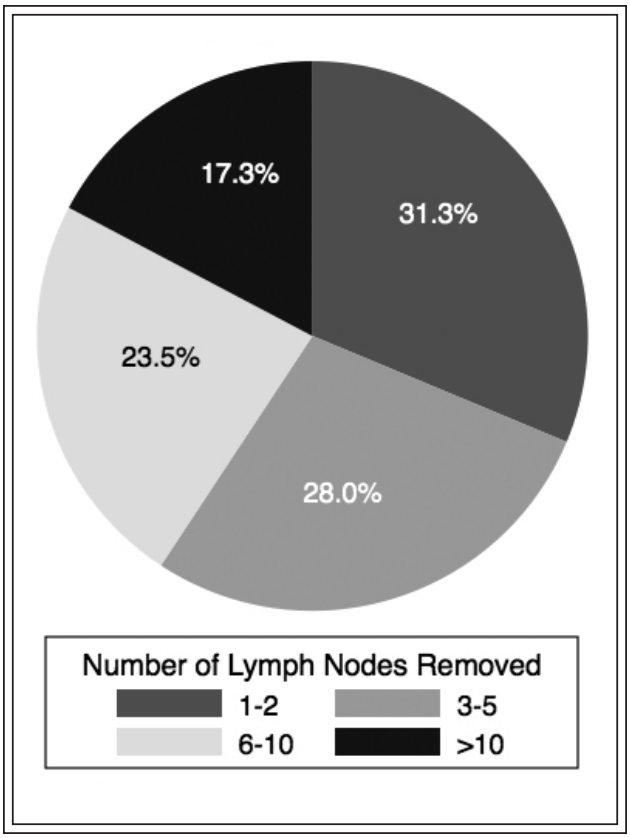

Figure 2. Breakdown of extent of lymph node dissection being performed (n = 5,856).

Discussion

In the present study, 1.1% of the patients diagnosed with GS 6 disease preoperatively that underwent LND were found to have lymph node positive disease. While this is more than double the rate from a recent nationwide study, in which 0.05% of patients had LNI[7] it appears to be in the range reported by some single center and multicenter studies of 0.08% to over 3%.[6,8,11,12] Node positive patients also had a greater proportion of black patients, elevated PSA, higher T3/T4 pathological stage, and a higher percentage of Gleason upgrades than patients with pathology proven lymph node negative disease. Advanced age and more advanced stage disease have previously been identified as risk factors for LNI.[7]

A potential explanation for the variation in percentage of GS 6 patients diagnosed with LNI is due to under-grading with the pre treatment biopsy. The data in this study show that approximately 50% of the patients who underwent LND, and almost 90% who were diagnosed as N+, were later upgraded compared to their initial biopsy specimen. This coincides with other studies that have demonstrated the rate of GS6 upgrade to be between 20%-60%.[13-18] Two proposed explanations for the high rate of subsequent upgrading are sampling errors (most likely) and interpretational bias.[19]

Despite the well-documented low risk of LNI in GS 6 patients, over 35% of patients underwent pelvic LND (PLND) in this national sample. The extent of LND performed varies according to surgeon preference and can range from a limited to an extended dissection. While the incidence of LNI has been shown to be more than double in those patients undergoing extended LND procedures, it is also a more complex procedure and carries with it more than two-fold greater risk of intraoperative and postoperative complications than limited or standard LND.[20,21] Briganti et al found that of 767 patients who underwent extended PLND, 18.9% had complications while only 7.3% of 196 who underwent standard PLND experienced complications. In another single institution study, McDowell et al found that 22% of 217 PLND patients had complications.[22] Moreover, Kavoussi et al showed that 15% of 356 standard LND patients had complications with the most common being vascular injury, visceral injury and genitourinary problems.[23]

In the present article, a surgery with even 1 removed LN was assigned into the LND group. This certainly affects the ability to evaluate a true prevalence of LN positive disease and may have artificially lowered the rate of LN involvement, possibly affecting our conclusions. While there is no standardized template for the LND or even clear indications for performing a node dissection for patients with preoperative GS 6 disease, a limited node "sampling" with an average of 6 nodes removed may not adequately represent the likelihood of LN involvement. When performing additional analysis with evaluation of patients who had at least 10 nodes removed (1,193 patients), we have identified the rate of the LN positivity to be 2.6%, consistent with prior studies suggesting a more extended LND as a routine template. In Briganti's work, the extended PLND resulted in 11.3% of positive LN versus only 3.7% in limited PLND.[20] Nevertheless, even after focusing on a more "extended" LND in our cohort and such a low rate of node positive disease questions any LND role in this population.

In addition, our findings may have implications for treatment as options vary significantly for patients with GS 6 versus higher-grade disease. Gleason 6 disease is a critical component of most active surveillance protocols.[24,25] Klotz et al showed that the 10-year overall survival rate was the same for

patients who underwent active surveillance and radical prostatectomy, thus, emphasizing the importance of a correct Gleason grading as unwarranted prostatectomy can have severe implications for quality of life. The increased utilization of MRI fusion biopsies, rather than standard TRUS biopsies, may help further stratify at risk patients, as suspicious lesions are also biopsied as opposed to standard random protocols resulting in a lesser upgrading on a final specimen.[26,27] It is possible that with improved imaging and decreased chance of upgrading more surgeons would feel comfortable omitting the LND.

In this study we found a significantly higher number of positive cores on biopsy between patients who underwent LND compared to those without LND. Briganti et al found that the number or percentage of positive cores significantly improved the predictive accuracy of GS, PSA, and clinical stage on rate of LNI. On multivariate analysis, positive cores were a more significant predictor than GS, however, it failed to reach independent predictor status.[28] No other studies to our knowledge have demonstrated the predictive nature of number of positive cores and propensity for LNI. Unfortunately, from this current analysis there is not a clear benchmark that can be established for number of positive cores on prostate biopsy that might indicate a patient will benefit from a LND, but there is a correlation with higher number of positive cores and lymph node positivity. Nevertheless, despite the fact that a GS upgrade on final pathology comprised 47.5% of our cohort and the concern for Gleason upgrading is often cited as the reason for performing LND, when looking at patients found to have only GS 6 on prostate biopsy, only 1.1% of patients undergoing LND were found to have LNI.

A recent study utilized the SEER database to analyze the prevalence of LNI in patients with GS 6 disease on final pathology.[7] There is one major difference between that study and the present analysis of the SEER database. Liu et al identified patients with GS 6 disease on final pathology compared to our patients that had GS on initial biopsy. The decision to proceed or not with LND is based on the biopsy before the surgery, and that was the exact question that we asked: how many patients with Gleason 6 on biopsy would have LNI? In our cohort, only 12 patients with Gleason 6 on the final pathology (0.1%) and only 1.1% among all patients that had Gleason 6 on biopsy had LNI. Similar to Liu et al, we found that patients who underwent LND had higher clinical T2 and more pathological T3 and T4 stage disease. In addition, the higher stage disease was present for those patients with LNI as well. Liu et al also analyzed PSA data and found a significant difference in patients who underwent LND versus those that did not (5.3 versus 5 ng/dl) and those with LNI and those without (5.75 versus 5.3). Unfortunately this PSA information has been withdrawn from the SEER datasets and cannot be applied to present analysis. Again, their analysis did not have information regarding number of biopsy cores taken, nor number of positive cores for malignancy as their study was based only on final pathology and did not include biopsy information.

As with any SEER analysis, this study is retrospective and reliant on proper database coding and data entry. There is a lack of centralized pathology review, which would be important in standardizing the GS of initial biopsy specimen. Finally, the template for LND is not well defined and the review of any LN qualified for assignment into the LN group (although the finding did not change after increasing the node count to at least 10). Despite several shortcomings, this study still represents a nationwide sample of practice patterns for surgical management of Gleason 6 prostate cancer. Even though there is a very low risk of node positive disease, a large proportion of patients still undergo LND.

Conclusion

LNDs are still being performed in a large number of patients with preoperative Gleason 6 disease. Despite a large percentage of Gleason upgrade in these patients on final pathology, only a small percentage of patients have nodal metastases at time of surgery in this nationwide cohort. This furthers the question of whether LND is warranted in preoperative Gleason 6 patients, as the risk of morbidity from LND may overweigh the risks of searching for nodal disease. □

References

1. Brawley OW. Prostate cancer epidemiology in the United States. *World J Urol* 2012;30(2):195-200.
2. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012;157(2):120-134.
3. Silverberg E. Cancer statistics, 1980. *CA Cancer J Clin* 1980;30(1): 23-38.
4. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017;67(1):7-30.
5. Egevad L, Granfors T, Karlberg L, Bergh A, Stattin P. Prognostic value of the Gleason score in prostate cancer. *BJU Int* 2002;89(6): 538-542.

6. Allaf ME, Palapattu GS, Trock BJ, Carter HB, Walsh PC. Anatomical extent of lymph node dissection: impact on men with clinically localized prostate cancer. *J Urol* 2004;172(5 Pt 1): 1840-1844.
7. Liu JJ, Lichtensztajn DY, Gomez SL et al. Nationwide prevalence of lymph node metastases in Gleason score 3 + 3 = 6 prostate cancer. *Pathology* 2014;46(4):306-310.
8. Ross HM, Kryvenko ON, Cowan JE, Simko JP, Wheeler TM, Epstein JI. Do adenocarcinomas of the prostate with Gleason score (GS) </=6 have the potential to metastasize to lymph nodes? *Am J Surg Pathol* 2012;36(9):1346-1352.
9. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. *BJU Int* 2013;111(5):753-760.
10. Eifler JB, Feng Z, Lin BM et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. *BJU Int* 2013;111(1):22-29.
11. Birkhahn M, Penson DF, Cai J et al. Long-term outcome in patients with a Gleason score </= 6 prostate cancer treated by radical prostatectomy. *BJU Int* 2011;108(5):660-664.
12. Abdollah F, Schmitges J, Sun M et al. Head-to-head comparison of three commonly used preoperative tools for prediction of lymph node invasion at radical prostatectomy. *Urology* 2011;78(6):1363-1367.
13. Fukagai T, Namiki T, Namiki H, Carlile RG, Shimada M, Yoshida H. Discrepancies between Gleason scores of needle biopsy and radical prostatectomy specimens. *Pathol Int* 2001;51(5):364-370.
14. Gofrit ON, Zorn KC, Taxy JB et al. Predicting the risk of patients with biopsy Gleason score 6 to harbor a higher grade cancer. *J Urol* 2007;178(5):1925-1928.
15. King CR, McNeal JE, Gill H, Brooks JD, Srinivas S, Presti JC Jr. Reliability of small amounts of cancer in prostate biopsies to reveal pathologic grade. *Urology* 2006;67(6):1229-1234.
16. Pinthus JH, Witkos M, Fleshner NE et al. Prostate cancers scored as Gleason 6 on prostate biopsy are frequently Gleason 7 tumors at radical prostatectomy: implication on outcome. *J Urol* 2006;176(3):979-984; discussion 984.
17. San Francisco IF, DeWolf WC, Rosen S, Upton M, Olumi AF. Extended prostate needle biopsy improves concordance of Gleason grading between prostate needle biopsy and radical prostatectomy. *J Urol* 2003;169(1):136-140.
18. Sved PD, Gomez P, Manoharan M, Kim SS, Soloway MS. Limitations of biopsy Gleason grade: implications for counseling patients with biopsy Gleason score 6 prostate cancer. *J Urol* 2004;172(1):98-102.
19. Gleason DF. Histologic grading of prostate cancer: a perspective. *Hum Pathol* 1992;23(3):273-279.
20. Briganti A, Chun FK, Salonia A et al. Complications and other surgical outcomes associated with extended pelvic lymphadenectomy in men with localized prostate cancer. *Eur Urol* 2006;50(5):1006-1013.
21. Silberstein JL, Derweesh IH, Kane CJ. Lymph node dissection during robot-assisted radical prostatectomy: where do we stand? *Prostate Cancer Prostatic Dis* 2009;12(3):227-232.
22. McDowell GC, 2nd, Johnson JW, Tenney DM, Johnson DE. Pelvic lymphadenectomy for staging clinically localized prostate cancer. Indications, complications, and results in 217 cases. *Urology* 1990;35(6):476-482.
23. Kavoussi LR, Sosa E, Chandhoke P et al. Complications of laparoscopic pelvic lymph node dissection. *J Urol* 1993;149(2): 322-325.
24. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol* 2010;28(1):126-131.
25. van As NJ, Norman AR, Thomas K et al. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. *Eur Urol* 2008;54(6): 1297-1305.
26. Canfield SE, Kibel AS, Kemeter MJ, Febbo PG, Lawrence HJ, Moul JW. A guide for clinicians in the evaluation of emerging molecular diagnostics for newly diagnosed prostate cancer. *Rev Urol* 2014;16(4):172-180.
27. Ghai S, Trachtenberg J. MRI-guided biopsies and minimally invasive therapy for prostate cancer. *Indian J Urol* 2015;31(3): 209-216.
28. Briganti A, Karakiewicz PI, Chun FK et al. Percentage of positive biopsy cores can improve the ability to predict lymph node invasion in patients undergoing radical prostatectomy and extended pelvic lymph node dissection. *Eur Urol* 2007;51(6): 1573-1581.