Omission of Lymphadenectomy in Low Risk Prostate Cancer

ANGELO NASELLI[1], ROSSANA ANDREATTA[1], CARLO INTROINI[1], VINCENZO FONTANA[2] and PAOLO PUPPO[1]

[1]Urology Unit, Surgical Oncology Department and [2]Epidemiology and Biostatistics Unit, Epidemiology and Prevention Department, National Institute for Cancer Research, Genoa, Italy

Abstract. *The aim of the present study was to evaluate if lymphadenectomy could be safely spared in low risk prostate cancer (PC) patients. Patients and Methods: From 5/1998 to 10/2005, 100 patients with low risk prostate cancer who had undergone radical prostatectomy (RP) and did not have positive surgical margins were selected. The series included 34 patients submitted to lymphadenectomy including the iliac and obturatory nodes without documented nodal metastasis. Results: Fifteen patients experienced a biochemical relapse (BR) at a median follow-up of 1.7 years. The pathological stage and not removing the nodes were both significant predictors of biochemical relapse (p-value=0.008 and 0.018) in univariate analysis. Adjusting for baseline imbalances through the Cox's regression model, a relative risk of BR which was more than five-fold higher in patients who had not been subjected to lymphadenectomy (p-value <0.05) was estimated. Conclusion: This observational investigation suggests that lymphadenectomy may not be safely spared in low risk prostate cancer patients.*

It is recognized that radical prostatectomy (RP) provides a concrete chance of cure for clinically localized prostate cancer (PC) (1, 2). However, the definition "clinically localized" PC harbors patients with different prognoses. Prostate specific antigen (PSA) ≤10 ng/mL, clinical stage T1c-T2a, biopsy Gleason score (GS) ≤6 and no primary GS pattern of 4 are the clinical features that define a subgroup of "clinically localized" PCs and imply a low risk of progression after curative treatment (3, 4). Nomograms show that low risk PCs are associated with nodal metastases in about 1-3% of the patients and, therefore, it is thought that lymphadenectomy can be safely spared (5-7). The database of RPs performed in our centre was analyzed to find out if low risk patients who had undergone lymphadenectomy resulting in pN0 had the same outcome with patients who had not undergone lymphadenectomy.

Correspondence to: Dr. Angelo Naselli, Urology Unit, Surgical Oncology Department, National Institute for Cancer Research, Largo Rosanna Benzi 10, 16132 Genoa, Italy. Tel: +390105600548, Fax: +390105600283, e-mail: angelo.naselli@auro.it

Key Words: Prostate cancer, radical prostatectomy, risk assessment, Cox's regression.

Patients and Methods

Patient selection. Patients were selected from a prospectively collected database of RPs. Those whose operations were performed before 1998 (before the introduction of modern TNM staging), patients with incidental cancer or who had received neo- or adjuvant therapy or had detectable PSA after surgery or at <90 days follow-up were excluded from the present analysis. The inclusion criteria were PSA ≤10 ng/mL, biopsy GS of 6 or less and clinical stage T1c or T2a, negative surgical margins and no lymph node metastasis after pathological examination. One hundred patients were finally selected. Between 5/1998 and 10/2005, 34 patients had undergone RP with lymphadenectomy (the pN0 group) and 66 patients without lymphadenectomy (the pNx group). An open retropubic RP was performed in all cases. Surgical excision routinely included the iliac and obturatory nodes, the median number of nodes removed in the series of selected patients was 11, range 7-18. Patients with nodal metastasis (the LNE group) or positive surgical margins (LNE and no-LNE groups) were excluded from the analysis. Biochemical relapse (BR) was defined as two consecutive increasing PSA levels >0.2 ng/mL (8). Follow-up ended with the last visit or when a BR occurred.

Statistical analysis. Apart from lymph node excision (LNE) and pathological stage (PS), the other analyzed prognostic factors were age at surgery (≤60; 61-67; ≥67), year of surgery (≤2002; 2003-2004; >2004), biopsy GS (≤5; =6), preoperative PSA (≤5.8; 5.9-7.8; >7.8) and pathological GS (≤5, =6, ≥7), which were categorized to obtain homogenous sizes of patient subgroups. The correlation between each prognostic factor and LNE was expressed in terms of odds ratio (OR) and statistically evaluated using the Chi-square test. The influence of each onset characteristic on biochemical relapse-free survival (BRFS) was evaluated by the Kaplan-Meier method and statistically assessed using the log-rank test (LT) (9). Also, the joint effect of all prognostic factors on BRFS was estimated by the proportional hazards Cox's regression model (9), and related regression coefficients were used to calculate the hazard ratio (HR), a specific relative risk index. In order to highlight the prognostic magnitude of LNE and its degree of dependence on imbalances in the other onset characteristics, several Cox's models were fitted, by adding, removing or replacing terms in the regression equation.

In this context, the reference model was defined by LNE alone, while the full model included all prognostic factors. The percent change in HR (ΔHR%) was used as an index of prognostic independence; the higher the change, the greater the dependence. The Akaike Information Criterion (AIC) was applied as an index of model selection. According to the AIC the best model is one which has the lowest value (9). Changes were calculated with respect to the reference model. The statistical significance of each model and each factor included in the model was evaluated by the likelihood ratio test (LRT). Additionally, the proportional hazards assumption was checked both graphically, by plotting log-minus-log survival probabilities against follow-up time, and formally, by performing the Grambsch-Therneau test (10). Finally, regression diagnostics were applied to highlight the data points able to influence unduly the modeling results (10). For each absolute or relative risk index, the corresponding 95% confidence limits (95% CLs) were also computed. All above-mentioned analyses were carried out using Stata statistical software (11).

Results

The correlation between LNE and all other prognostic factors considered in this investigation are described in Table I. A clear and statistically significant upward trend by year of surgery in the proportion of pNx patients was found, before 2003 38.2% patients were in the pNx group, afterwards that group became 80.3% (p-value <0.001). Heterogeneities in LNE distribution were also found by biopsy GS (p-value=0.011) and pathological GS (p-value=0.001). Only slight or null correlations were shown for pre-operative PSA (p-value=0.086), age at surgery (p-value=0.937) and pathological stage (p-value=0.958). Table II shows the 1-, 3-, and 5-year BRFS, along with the log-rank test and corresponding p-values. The median follow-up time was 1.7 years (inter-quartile range=0.7-3.3 years) in the whole group, 3.3 years (inter-quartile range=1.5-6.5 years) in the pN0 group and 1.4 years (inter-quartile range=0.8-2.1 years) in the pNx group. Overall, during the study period 15 out of 100 patients (15.0%) experienced a BR, giving rise to a BRFS probability of 65.6% (95% CLs=47.6%-78.8%) after four years of follow-up. Only PS and LNE were significant predictors of BR (p-value=0.008 and p-value=0.018, respectively) with a higher risk for pT3 and pNx patients (Table II and Figure 1).

Table III reports the HR for LNE (pN0 patients as the reference group), along with the corresponding 95% CLs and p-values, AIC and their variations (ΔHR% and ΔAIC) with respect to model 1. Given the high correlation between biopsy and pathological GS, just the latter was considered for multivariate analyses. By and large, the pNx patients fared constantly worse than the pN0 patients, in that they showed an increased risk of BR ranging from 3.75 to 5.65. In six out of seven models, changes in HRs greater than 10% were observed, indicating that baseline imbalances in the concomitant characteristics doubtless played a key role in determining the magnitude of the LNE-specific BR risk. On the basis of the AIC the best models appeared to be model 3 (ΔAIC=–3.590) and model 7 (ΔAIC=–3.652), both showing very similar relative risk estimates (HR=5.40, 95% CLs=1.35-21.56 and HR=5.65, 95% CLs=1.44-22.11, respectively). However, the small sample size and the very low BR frequency (15.0%) gave rise to quite imprecise HR estimates.

Finally, goodness-of-fit techniques demonstrated neither large violations of the proportional hazards assumption (Grambsch-Therneau test p-value >0.05 for all models) nor remarkably influential data points.

Table I. *Lymph node excision and other patient characteristics.*

Factors and levels	Lymph node excision				
	pN0 N (%)	pNx N (%)	OR	95%CLs	p-value
Year of surgery					<0.001
≤2002	21 (61.8)	13 (19.7)	1.00	-	
2003-2004	8 (23.5)	36 (54.5)	7.27	2.59-20.41	
>2004	5 (14.7)	17 (25.8)	5.49	1.63-8.48	
Age at surgery					0.937
≤60 years	12 (35.3)	21 (31.8)	1.00	-	
61-67 years	11 (32.4)	23 (34.9)	1.20	0.44-3.28	
>67 years	11 (32.4)	22 (33.3)	1.14	0.42-3.15	
Pre-operative PSA level					0.086
≤5.8	10 (29.4)	23 (34.9)	1.00	-	
5.9-7.8	8 (23.5)	26 (39.3)	1.41	0.48-4.19	
>7.8	16 (47.1)	17 (25.8)	0.46	0.17-1.27	
Biopsy Gleason score					0.011
≤5	20 (58.8)	21 (31.8)	1.00	-	
=6	14 (41.2)	45 (71.2)	3.06	1.30-7.21	
Pathological Gleason score					0.001
≤5	16 (47.1)	9 (13.6)	1.00	-	
=6	11 (21.3)	39 (59.1)	6.30	2.19-18.12	
≥7	7 (20.6)	18 (27.3)	4.57	1.38-15.11	
Pathological stage					0.958
pT2	30 (88.2)	58 (87.9)	1.00	-	
pT3	4 (11.8)	8 (12.1)	1.03	0.29-3.72	
Total	34 (100.0)	66 (100.0)	-	-	-

N: number of patients; OR: odds ratio; 95% CLs: 95% confidence limits for OR; p-value: significance level of Chi-square test; pN0: lymphadenectomy group; pNx: no lymphadenectomy group.

Discussion

It is increasingly accepted that a low risk prostate cancer has an "acceptably" low risk of nodal metastasis, and, therefore, lymphadenectomy could be safely avoided, when PSA ≤10 ng/mL, biopsy GS up to 6 and clinical stage T1c or T2a are the characteristics that define the low risk category.

Table II. *Univariate biochemical relapse-free survival analysis estimated by the Kaplan-Meier method.*

Factors and levels	N	R (%)	Biochemical relapse-free survival probability %			LT	*p*-value
			1 year (95% CLs)	3 years (95% CLs)	5 years (95% CLs)		
Age at surgery						1.81	0.405
≤60 years	33	6 (18.2)	96.9 (79.8-99.6)	74.3 (42.2-90.3)	49.5 (17.1-75.6)		
61-67 years	34	5 (14.7)	96.3 (76.5-99.5)	83.4 (54.9-94.6)	58.4 (22.1-82.5)		
> 67 years	33	4 (12.1)	100.0 (-)	88.1 (67.1-96.0)	80.7 (54.4-92.8)		
Year of surgery						3.76	0.153
≤2002	34	9 (26.5)	100.0 (-)	88.0 (71.0-95.3)	69.8 (49.6-83.1)		
2003-2004	44	5 (11.4)	97.7 (84.6-99.7)	80.5[1] (56.5-92.1)	80.5[1] (56.5-92.1)		
>2004	22	1 (4.6)	95.22 (70.7-99.2)	95.2[2] (70.7-99.2)	95.2[2] (70.7-99.2)		
Pre-operative PSA level						2.80	0.247
≤5.8	33	2 (6.1)	96.9 (79.8-99.6)	88.1 (55.0-97.3)	88.1 (55.0-97.3)		
5.9-7.8	34	6 (17.7)	96.7 (79.8-99.6)	88.0 (66.3-96.1)	65.2 (35.9-83.6)		
>7.8	33	7 (21.2)	100.0 (-)	73.4 (66.1-88.4)	45.9 (13.8-73.6)		
Biopsy Gleason score						0.03	0.856
≤5	41	8 (19.5)	100.0 (-)	81.0 (59.5-91.8)	63.6 (38.9-80.6)		
=6	59	7 (11.9)	96.2 (85.6-99.1)	84.8 (65.7-93.7)	68.0 (38.6-85.5)		
Pathological Gleason score						0.87	0.647
≤5	25	4 (16.0)	100.0 (-)	79.9 (49.3-93.1)	71.9 (40.8-88.6)		
=6	50	5 (10.0)	97.6 (83.9-99.6)	93.1 (73.8-98.3)	51.7 (14.2-80.1)		
≥7	25	6 (24.0)	96.0 (74.8-99.4)	73.6 (47.0-88.3)	63.1 (32.6-82.7)		
Pathological stage						7.14	0.008
pT2	88	10 (11.4)	100.0 (-)	89.2 (75.7-95.4)	69.1 (48.5-82.8)		
pT3	12	5 (41.7)	83.3 (48.2-95.6)	42.3 (8.1-74.5)	42.3 (8.1-74.5)		
Lymph node excision						5.61	0.018
pN0	34	4 (11.8)	100.0 (-)	91.3 (69.5-97.6)	80.5 (55.6-92.3)		
pNx	66	11 (16.7)	96.6 (86.9-99.1)	78.5 (60.3-89.0)	45.8 (16.7-71.1)		
Total	100	15 (15.0)	97.8 (91.4-99.4)	82.8 (69.6-90.6)	65.6 (47.6-78.8)		

N: number of patients; R: number of relapsed patients; 95% CLs: 95% confidence limits for the relapse-free survival probability; LT: log-rank test; *p*-value: two-tailed significance level for LT. Notes – (1) 2.5 and (2) 0.8 year relapse-free survival probability.

Partin *et al.* (5), Crawford *et al.* (12) and Han *et al.* (13) observed about 1% of nodal metastasis among low risk PCs from the Johns Hopkins Hospital series of RPs. In the same series, Haese *et al.* showed that the absence in any biopsy of a 4 or 5 Gleason pattern was associated with a 2.7% share of nodal metastasis, irrespective of PSA or clinical stage (14).

Bhatta Dhar *et al.* analized the records of 336 consecutive low risk patients and did not find any difference in terms of

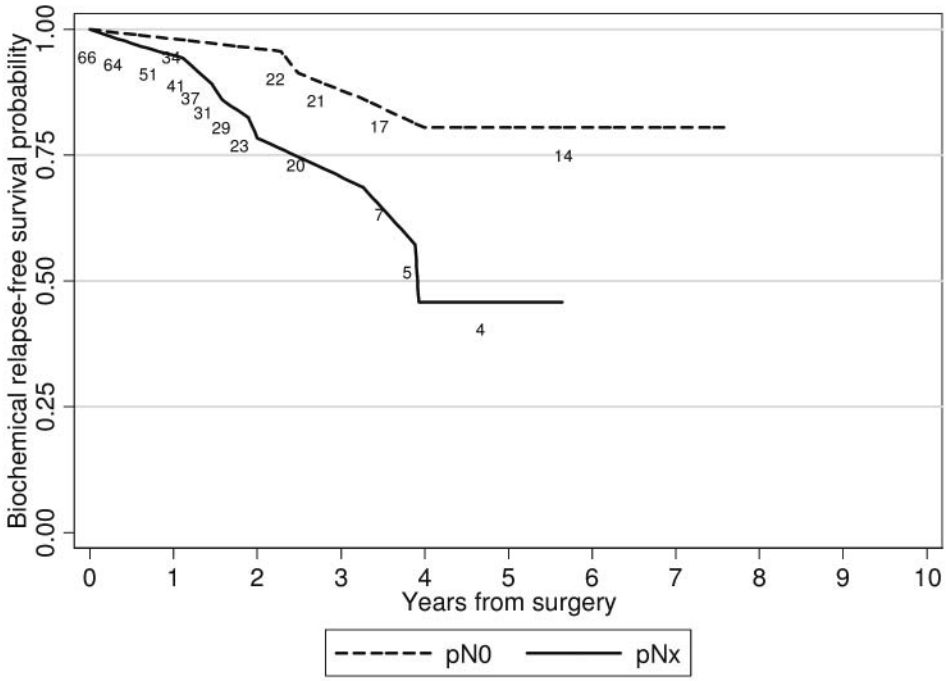

Figure 1. *Numbers under the curves represent patients at risk immediately prior to each biochemical relapse time.*

Table III. *Relative risks of biochemical relapse for lymph node excision (pNx patients versus pN0 patients) and model performance according to prognostic factors entered in the Cox's regression model.*

Model	Prognostic factors entered the model	HR	95% CLs	*p*-value	DHR%	AIC	DAIC
1 (reference)	LNE alone	3.88	1.18-12.72	0.025	0.0	107.917	0.0
2	LNE + AAS + YOS	4.29	1.18-15.45	0.027	10.6	107.833	–0.084
3	LNE + AAS + YOS + PS	5.40	1.35-21.56	0.017	39.2	104.327	–3.590
4	LNE + AAS + YOS + GS	3.75	1.01-14.05	0.049	–3.4	109.302	1.385
5	LNE + AAS + YOS + PSA	4.72	1.27-17.50	0.020	21.7	108.575	0.658
6	LNE + AAS + YOS + PS + GS	4.89	1.16-20.70	0.031	26.0	106.159	–1.758
7	LNE + AAS + YOS + PS + PSA	5.65	1.44-22.11	0.013	45.6	104.265	–3.652
8	LNE + AAS + YOS + PS + GS + PSA	5.49	1.32-22.81	0.019	41.5	106.247	–1.670

HR: hazard ratio (relative risk), 95% CLs: 95% confidence limits for HR, *p*-value: two-tailed significance level of the likelihood ratio test, DHR%: percent difference in HR, AIC: Akaike information criterion, DAIC: absolute difference in AIC, LNE: lymph node excision, AAS: age at surgery, YOS: year of surgery, PS: pathological stage, PSA: preoperative PSA, GS: pathological Gleason score.

BR between the group who had undergone LNE and the group who had not (6). Salomon *et al.* came to the same conclusion comparing 43 low risk patients who had undergone perineal prostatectomy alone to 25 patients who had undergone radical retropubic prostatectomy and lymphadenectomy (7).

Following these studies, given the poor potential benefit of lymphadenectomy in the low risk category, it was suggested that it could be avoided to reduce complications and costs (15).

However, there are some criticisms. Firstly, some papers have shown a higher occurrence of nodal metastasis, up to 10%, in low risk patients when an extended lymphadenectomy was performed (16-19). Therefore, the real frequency of nodal metastasis could probably be higher than expected in series of patients subjected to limited lymphadenectomy (5, 12-14). Burkhard *et al.* reported a relative frequency of nodal metastasis of 12% in cases with PSA <10 ng/mL and of 17% in cases of GS≤6 (16). In a series of patients with PSA <10 ng/mL and biopsy GS≤6, the proportion of pN+

patients was 6.8% in cases with a positive biopsy in one lobe and 10.7% in cases with a positive biopsy in both lobes (17). When the preoperative serum PSA was less than 10.6 ng/mL, the Gleason sum 6 or less and the clinical stage T2a or less, the proportion of nodal metastasis reported in another study was 2.7% (18). Compared to limited lymph node dissection, extended pelvic lymphadenectomy appears to identify men with positive lymph nodes more frequently. A median of 11.6 *vs.* 8.9 nodes was removed respectively in the extended and standard dissection (p-value <0.001), while the occurrence of nodal metastasis was respectively 3.2% *vs.* 1.1% (p-value <0.001) (19).

Secondly, lymphadenectomy can increase significantly the disease-free survival in patients with a low burden of nodal metastasis (20-23). Patients with low tumor bulk and just one positive lymph node had survival probabilities comparable to matched controls after a mean follow-up of 5 years (20). Men with single node disease who were treated with immediate adjuvant hormone therapy had a more favorable prognosis than men with larger nodal involvement treated in a similar fashion (21). A prolonged survival was reported in patients with two metastatic lymph nodes or less who underwent extensive pelvic node dissection even without adjuvant androgen deprivation and correlation between the number of diseased nodes removed and disease progression was found (22). Twenty-one men (23%) with lymph node metastases and prostatectomy GS 7 or less were free of disease at a median follow up of 7 years (23).

Thirdly, the impact of node excision itself, irrespective of the presence or absence of nodal metastasis, on the disease free survival has occasionally been evaluated (6, 7, 24). Salomon *et al.* (7) prospectively evaluated the influence of non-dissection of pelvic lymph nodes on tumor progression in perineal prostatectomies. Forty three patients (group 1) did not undergo LNE because their preoperative PSA level was below 10 ng/mL and the GS of their positive biopsies was below 7 and they were compared with 25 patients who had retropubic surgery with LNE and the same preoperative PSA and GS criteria. No differences in preoperative characteristics were observed between the groups but the actuarial 5-year recurrence-free survival probability was 78% in group 1 and 80% in group 2 (p-value >0.05).

Bhatta Dhar *et al.* (6) reviewed the records of 336 patients with favorable tumor characteristics (prostate-specific antigen 10 ng/mL or less, biopsy GS≤6, and clinical Stage T1 or T2), not receiving adjuvant or neoadjuvant therapy, in whom LNE was performed (n=140) or omitted (n=196). The 6-year BRFS probability showed no significant differences between the groups. Unfortunately, there was a statistically significant different proportion of extra capsular extension, the no-LNE group 23% *versus* the LNE group 34% (p-value=0.02). Masterson *et al.* found that in patients without lymph node involvement, the number of nodes removed correlated significantly with biochemical relapse free survival probability (24).

Surprisingly, in the present study avoiding LNE resulted in an increased risk of BR in both univariate and multivariate analysis, although baseline imbalances in patient characteristics showed a remarkable importance in determining the magnitude of difference in relapse rates (Table I). In particular, the correlation between LNE and year of surgery is easily explained in that the procedure was virtually abandoned in low risk prostate cancer cases after 1999. In addition, the significant relationship between GS indices and LNE was undoubtedly due to the higher probability of being GS≥6 for the pNx patients than the pN0 patients. However, pathological GS was not a predictor of BR in either univariate (HR=1.37; 95% CLs=0.84-2.23) or multivariate analysis (HR=1.04; 95% CLs=0.57-1.92).

The present investigation had several limitations. Firstly, it was not a randomized study but consisted essentially of an observational series of PC cases at low risk of BR. As already stated, these circumstances brought about imbalances in baseline characteristics, even if taken into consideration through multivariate analysis. Secondly, each of the eight models of multivariate analysis reached statistical significance only apparently. According to Bonferroni (25), the p-value to be considered significant is 0.05/8. The low number of available patients (100), the short median follow-up (1.7 years) and, more importantly, the low number of BR (15) prevented our analysis from having satisfactory statistical power.

Moreover, it is well-known that PSA relapse may not translate into mortality from prostate cancer for all patients. It was not intended to change guidelines on prostate cancer treatment with this study, but to further explore an assumption based on only two studies concerning pNx and pN0 patients (6, 7) and on many indirect observations such as the incidence of nodal metastasis reported in nomograms.

Conclusion

This observational investigation suggests that lymphadenectomy may not be safely spared in low risk prostate cancer patients due to the increased risk of BR. Further investigation is necessary to confirm the findings of the present analysis before lymphadenectomy is left behind.

References

1 Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, Spangberg A, Busch C, Nordling S, Garmo H, Palmgren J, Adami HO, Norlen BJ and Johansson JE; Scandinavian Prostate Cancer Group Study No. 4: Radical prostatectomy *versus* watchful waiting in early prostate cancer. N Engl J Med *352*: 1977-1984, 2005.

2 Tewari A, Johnson CC, Divine G, Crawford ED, Gamito EJ, Demers R and Menon M: Long-term survival probability in men with clinically localized prostate cancer: a case-control, propensity modeling study stratified by race, age, treatment and comorbidities. J Urol *171*: 1513-1519, 2004.
3 D'Amico AV, Whittington R, Malkowicz SB, Cote K, Loffredo M, Schultz D, Chen MH, Tomaszewski JE, Renshaw AA, Wein A and Richie JP: Biochemical outcome after radical prostatectomy or external beam radiation therapy for patients with clinically localized prostate carcinoma in the prostate specific antigen era. Cancer *95*: 281-286, 2002.
4 Stephenson AJ, Scardino PT, Eastham JA, Bianco FJ Jr, Dotan ZA, Fearn PA and Kattan MW: Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst *98*: 715-717, 2006.
5 Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI and Pearson JD: Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology *58*: 843-848, 2001.
6 Bhatta-Dhar N, Reuther AM, Zippe C and Klein EA: No difference in six-year biochemical failure rates with or without pelvic lymph node dissection during radical prostatectomy in low risk pts with localized prostate cancer. Urology *63*: 528-531, 2004.
7 Salomon L, Hoznek A, Lefrere-Belda MA, Bellot J, Chopin DK and Abbou CC: Nondissection of pelvic lymph nodes does not influence the results of perineal radical prostatectomy in selected patients. Eur Urol *37*: 297-300, 2000.
8 Polascik TJ, Oesterling JE and Partin AW: Prostate specific antigen: a decade of discovery-what we have learned and where we are going. J Urol 162: 293-306, 1999.
9 Marubini E and Valsecchi MG: Analysing Survival Data from Clinical Trials and Observational Studies. Chichester: John Wiley & Sons, Inc., pp. 288-291, 1995.
10 Hosmer DW and Lemeshow S: Applied Survival Analysis. New York: John Wiley & Sons, Inc., pp. 93-216, 1999.
11 Stata Corp. Stata Statistical Software, Release 8.0. Survival Analysis and Epidemiological Tables. Stata Corporation, College Station, TX, 2003.
12 Crawford ED, Batuello JT, Snow P, Gamito EJ, McLeod DG, Partin AW, Stone N, Montie J, Stock R, Lynch J and Brandt J: The use of artificial intelligence technology to predict lymph node spread in men with clinically localized prostate carcinoma. Cancer *88*: 2105-2109, 2000.
13 Han M, Snow PB, Brandt JM and Partin AW: Evaluation of artificial neural networks for the prediction of pathologic stage in prostate carcinoma. Cancer *91(8 Suppl)*: 1661-1666, 2001.
14 Haese A, Epstein JI, Huland H and Partin AW: Validation of a biopsy-based pathologic algorithm for predicting lymph node metastases in patients with clinically localized prostate carcinoma. Cancer *95*: 1016-1021, 2002.
15 Clark T, Parekh DJ, Cookson MS, Chang SS, Smith ER Jr, Wells N and Smith JA Jr: Randomized prospective evaluation of extended *versus* limited lymph node dissection in patients with clinically localized prostate cancer. J Urol *169*: 145-147, 2003.
16 Burkhard FC, Bader P, Schneider E, Markwalder R and Studer UE: Reliability of preoperative values to determine the need for lymphadenectomy in patients with prostate cancer and meticulous lymph node dissection. Eur Urol *42*: 84-90, 2002.
17 Weckermann D, Wawroschek F and Harzmann R: Is there a need for pelvic lymph node dissection in low risk prostate cancer patients prior to definitive local therapy? Eur Urol *47*: 45-50, 2005.
18 Heidenreich A, Varga Z and Von Knobloch R: Extended pelvic lymphadenectomy in patients undergoing radical prostatectomy: high incidence of lymph node metastasis. J Urol *167*: 1681-1686, 2000.
19 Allaf ME, Palapattu GS, Trock BJ, Carter HB and Walsh PC: Anatomical extent of lymph node dissection: impact on men with clinically localized prostate cancer. J Urol *172*: 1840-1844, 2004.
20 Golimbu M, Provet J, Al-Askari S and Morales P: Radical prostatectomy for stage D1 prostate cancer. Prognostic variables and results of treatment. Urology *30*: 427-435, 1987.
21 Cheng L, Zincke H, Blute ML, Bergstralh EJ, Scherer B and Bostwick DG: Risk of prostate carcinoma death in patients with lymph node metastasis. Cancer *91*: 66-73, 2001.
22 Bader P, Burkhard FC, Markwalder R and Studer UE: Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure? J Urol *169*: 849-854, 2003.
23 Palapattu GS, Allaf ME, Trock BJ, Epstein JI and Walsh PC: Prostate specific antigen progression in men with lymph node metastases following radical prostatectomy: results of long-term follow-up. J Urol *172*: 1860-1864, 2004.
24 Masterson TA, Bianco FJ Jr, Vickers AJ, DiBlasio CJ, Fearn PA, Rabbani F, Eastham JA and Scardino PT: The association between total and positive lymph node counts, and disease progression in clinically localized prostate cancer. J Urol *175*: 1320-1324, 2006.
25 Bland JM: An Introduction to Medical Statistics, 3rd Ed. Oxford University Press, Oxford, UK, Chapter 9, pp.148-151, 2000.

Received June 5, 2007
Revised August 3, 2007
Accepted October 1, 2007