Use of Preoperative Plasma Endoglin for Prediction of Lymph Node Metastasis in Patients with Clinically Localized Prostate Cancer

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Abstract

Purpose: Current predictive tools and imaging modalities are not accurate enough to preoperatively diagnose lymph node metastases in patients with prostate cancer. The aim of the study was to evaluate whether preoperative plasma endoglin improves the prediction of lymph node metastases in patients with clinically localized prostate cancer.

Experimental Design: Endoglin levels were measured using a commercially available ELISA assay in banked plasma from 425 patients treated with radical prostatectomy and bilateral lymphadenectomy for clinically localized prostatic adenocarcinoma at two university hospitals between July 1994 and November 1997. Logistic regression analyses were undertaken to evaluate whether endoglin improves the accuracy of a standard preoperative model for prediction of lymph node metastasis and to build a predictive nomogram.

Results: Preoperative plasma endoglin levels were higher in patients with higher preoperative total serum prostate-specific antigen (PSA; Spearman correlation coefficient 0.296, $P < 0.001$), positive surgical margins ($P = 0.03$), higher pathologic Gleason sum ($P = 0.04$), and lymph node metastasis ($P < 0.001$). In a preoperative multivariable logistic regression analysis that included PSA and clinical stage, only preoperative endoglin (odds ratio, 1.17; 95% confidence interval, 1.09-1.26; $P < 0.001$) and biopsy Gleason sum (odds ratio, 18.57; 95% confidence interval, 1.08-318.36; $P = 0.04$) were associated with metastasis to lymph nodes. The addition of endoglin to a standard preoperative model (including PSA, clinical stage, and biopsy Gleason sum) significantly improved its accuracy for prediction of lymph node metastasis from 89.4% to 97.8% ($P < 0.001$).

Conclusions: Preoperative plasma endoglin improves the accuracy for prediction of pelvic lymph node metastasis in patients treated with radical prostatectomy for clinically localized prostate cancer by a statistically and clinically significant margin.

Prostate cancer is the most commonly diagnosed noncutaneous cancer affecting an estimated 218,890 men in 2007 and is the second leading cause of cancer-related death in men in the United States (1). Although local therapies with curative intent, such as radical prostatectomy and radiotherapy, result in durable disease control in most men with pathologically localized prostate cancer, the presence of pelvic lymph node metastases entails a poor prognosis. It is of paramount importance to have an accurate prediction of lymph node metastasis for treatment planning. Preoperative imaging modalities are not accurate enough to diagnose lymph node metastases (2), especially in low-risk patients. Unfortunately, pelvic lymphadenectomy is not routinely done in the current era with the advent of pure and robot-assisted laparoscopic radical prostatectomy. A quantitative and standardized blood marker that can predict the presence of clinically occult lymph node metastases could assist clinicians in identifying patients who should undergo pelvic lymphadenectomy.

Angiogenesis, the process of new blood vessel formation, is a well-established critical event in the initiation and progression of solid malignancies (3). The normal prostate secretes several angiogenesis-regulating factors (4). Prostate vasculature is an important regulator of the growth and regression of normal prostate tissue (5, 6). Similarly, prostate tumor growth is dependent on angiogenesis and prostate cancer growth is inhibited by antiangiogenic therapy (4, 6). Endoglin is a 180-kDa homodimeric transmembrane glycoprotein (7) that is highly expressed by human vascular endothelial cells (8).

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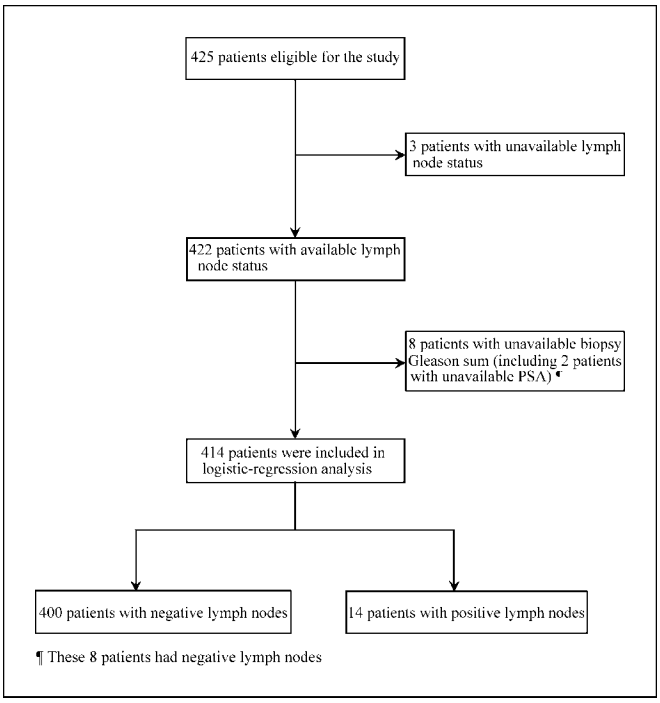

Fig. 1. Patient flow chart.

Functionally, endoglin, or CD105, is a cell surface coreceptor for transforming growth factor (TGF)-β1 and TGF-β3 (9) and modulates TGF-β signaling in several systems, including the prostate (10). Serum levels of endoglin are elevated in patients with metastatic colon and breast cancer (11, 12). To date, no study has evaluated blood levels of endoglin in prostate cancer patients.

We hypothesized that endoglin levels would be elevated in patients with pelvic lymph node metastases. Therefore, we assessed whether addition of preoperative plasma endoglin to a standard preoperative predictive model would improve the accuracy of the model for prediction of pelvic lymph node metastases in patients with clinically localized prostate cancer.

Materials and Methods

Patient population. All studies were undertaken with the approval and oversight of the Institutional Review Board. This retrospective study comprised 425 patients treated with radical prostatectomy and bilateral lymphadenectomy for clinically localized prostatic adenocarcinoma (clinical stages T_1 and T_2) during the period from July 1994 to November 1997 at two university hospitals who had plasma samples available and provided informed consent. The clinical stage was assigned by the operative surgeon according to the 1992 tumor-node-metastasis system. No patients were treated preoperatively with either hormonal or radiation therapy, and none had secondary cancers. Three patients did not have information about lymph node status. Eight patients did not have biopsy Gleason sum available. These eight patients had negative lymph nodes. Four hundred fourteen patients were left for final logistic regression analysis (Fig. 1). Serum total prostate-specific antigen (PSA) was measured by the Hybritech Tandem-R assay (Hybritech). Standard bilateral pelvic lymph node dissection (including external iliac and obturator lymph nodes) was done. Staff pathologists from each institution, who were blinded to clinical outcomes, examined all prostatectomy and lymphadenectomy specimens. Evaluation of radical prostatectomy specimens was done as previously described (13) in accordance with the guidelines of the College of American Pathologists (14).

Plasma endoglin measurements. Plasma samples were collected after a preoperative overnight fast on the morning of the day of surgery, at least 4 weeks after transrectal guided needle biopsy of the prostate. Blood was collected into Vacutainer CPT 8-mL tubes containing 0.1 mL of molar sodium citrate (Becton Dickinson Vacutainer Systems) and centrifuged at room temperature for 20 min at $1,500 \times g$. The top layer corresponding to plasma was decanted using sterile transfer pipettes. The plasma was immediately frozen and stored at -80°C in polypropylene cryopreservation vials (Nalgene, Nalge Nunc). For quantitative measurements of endoglin levels, we used a commercially available quantitative immunoassay (R&D Systems). Every sample was run in duplicate, and the mean was calculated for data analysis. Differences between the two measurements were minimal (intra-assay precision coefficients of variation equals $7.9 \pm 5.0\%$).

Statistical analysis. Continuous variables are reported as medians and interquartile range (IQR). Differences in endoglin levels across

Table 1. Association of preoperative plasma endoglin levels with clinical and pathologic features of 425 patients treated with radical prostatectomy and bilateral lymphadenectomy for clinically localized prostate cancer

	No. (%)	Median plasma endoglin level, ng/mL (IQR)	*P*
Total (%)	425 (100)	28.8 (18.7-37.5)	—
Clinical stage			
T_1	269 (63.3)	28.6 (19.3-36.3)	—
T_2	156 (36.7)	29.4 (18.0-39.8)	0.19*
Extraprostatic extension †			
Negative	282 (67.0)	28.2 (19.3-35.8)	—
Positive	139 (33.0)	30.6 (15.1-40.9)	0.21*
Seminal vesicle involvement †			
Negative	354 (84.1)	28.3 (19.3-36.1)	—
Positive	67 (15.9)	31.3 (13.9-45.0)	0.20*
Surgical margin status †			
Negative	331 (78.6)	28.0 (18.6-36.0)	—
Positive	90 (21.4)	31.9 (18.5-43.9)	0.03*
Biopsy Gleason sum ‡			
2-6	292 (70.0)	27.9 (19.2-35.9)	—
7	93 (22.3)	31.2 (18.3-39.8)	—
8-10	32 (7.7)	36.1 (14.1-51.4)	0.10§
Pathologic Gleason sum †			
2-6	199 (47.2)	27.3 (18.8-35.4)	—
7	180 (42.8)	28.7 (18.6-38.3)	—
8-10	42 (10.0)	33.8 (17.2-49.2)	0.04§
Lymphovascular invasion‖			
Negative	222 (88.8)	26.5 (18.1-33.3)	—
Positive	28 (11.2)	25.2 (13.8-53.9)	0.40*
Perineural invasion‖			
Negative	94 (37.6)	24.4 (17.5-32.8)	—
Positive	156 (62.4)	27.4 (17.9-35.8)	0.14*
Lymph node metastases¶			
Negative	408 (96.7)	27.9 (18.3-36.3)	
Positive	14 (3.3)	57.1 (51.4-67.3)	<0.001*

**P* value calculated from Mann-Whitney *U* test.
† Data on extraprostatic extension, seminal vesicle invasion, surgical margin status, and pathologic Gleason sum were not available in four patients.
‡ Biopsy Gleason sum was not available in eight patients.
§ *P* value calculated from Kruskal-Wallis test.
‖ Data on lymphovascular and perineural invasion were not available in 175 patients.
¶ Lymph node status was not available in three patients.

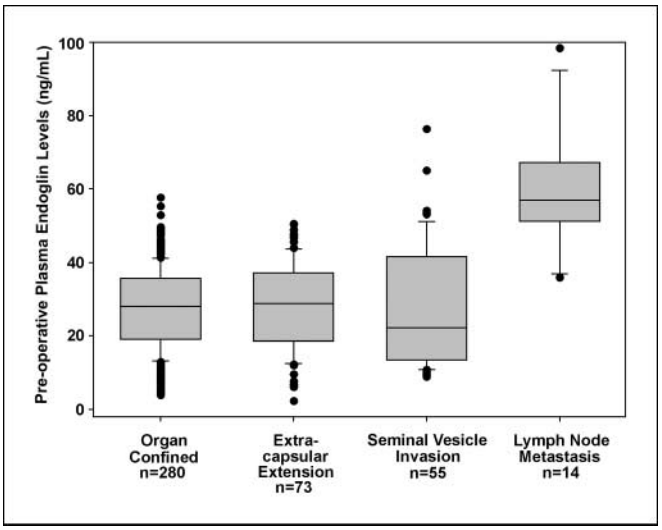

Fig. 2. Plots of the median and 10th, 25th, 75th, and 90th percentiles of preoperative plasma endoglin levels in radical prostatectomy patients stratified by mutually exclusive pathologic stages, displayed as vertical boxes with error bars.

categorical variables were assessed using the Mann-Whitney *U* test or the Kruskal-Wallis test. Univariable and multivariable analyses were done with logistic regression analysis. Risk was calculated with the use of odds ratios (OR) and 95% confidence intervals (95% CI). The goodness of fit of the models was assessed with a Hosmer-Lemeshow test based on deciles of probability. Multivariable logistic regression coefficients and constants were used to generate a prognostic nomogram for prediction of lymph node metastasis. Predictive accuracies of the multivariable logistic regression models were quantified using area under the receiver operating characteristic curve–derived analyses (15, 16). A value of 100% indicates perfect predictions, whereas 50% is equivalent to a toss of a coin. Internal validation was done using 200 bootstrap resamples with replacement to reduce overfit bias and for internal validation (17). Predictive accuracy estimates of the multivariable models were compared using the Mantel-Haenszel test. Calibration plots were generated to explore nomogram performance. Statistical significance in this study was set at a P value of <0.05. All reported P values are two sided. Analyses were done with Statistical Package for the Social Sciences version 13.0 (SPSS) or S-Plus Professional (MathSoft).

Results

Association of preoperative plasma endoglin levels with clinical and pathologic characteristics of prostate cancer. Median patient age was 61.1 years (IQR, 55.6-66.5). Median preoperative serum total PSA level and plasma endoglin level were 5.7 ng/mL (IQR, 3.7-8.7) and 28.8 ng/mL (IQR, 18.7-37.5), respectively. Overall, 27.6% of the patients had a total PSA of <4 ng/mL, 56.3% had a total PSA between 4 and 9.9 ng/mL, and 16.1% had a total PSA of ≥10 ng/mL. The clinical and pathologic characteristics of the patients and their association with preoperative plasma endoglin levels are shown in Table 1. Plasma endoglin levels were higher in patients with higher preoperative total PSA (Spearman correlation coefficient 0.296, $P < 0.001$), positive surgical margins ($P = 0.03$), higher pathologic Gleason sum ($P = 0.04$), and lymph node metastasis ($P < 0.001$).

Association of preoperative plasma endoglin levels with lymph node metastases. Four hundred twenty-two of 425 patients underwent pelvic lymphadenectomy at the time of prostatectomy. The median number of lymph nodes retrieved at radical prostatectomy was 6 (IQR, 4-9). Overall, 14 of 422 patients (3.3%) had positive lymph nodes. Plasma endoglin levels were significantly higher in patients with lymph node metastases compared with patients without lymph node metastases ($P < 0.001$; Fig. 2).

Results of univariable and multivariable logistic regression analyses are displayed in Table 2. In univariable analysis, endoglin had the highest accuracy for predicting lymph node metastasis (95.6%). In a multivariable logistic regression analysis that adjusted for the effects of standard preoperative features, preoperative plasma endoglin (OR, 1.17; 95% CI, 1.09-1.26; $P < 0.001$) and biopsy Gleason sum (OR, 18.57; 95% CI, 1.08-318.36; $P = 0.04$) were independent predictors of lymph node metastasis. The addition of endoglin to a standard

Table 2. Univariable and multivariable logistic regression analyses of preoperative features for the prediction of lymph node metastasis in 414 patients treated with radical prostatectomy and bilateral lymphadenectomy for clinically localized prostate cancer

Predictors	Univariable analyses			Multivariable analyses				P*
	OR (95% CI)	P †	PA (%) ‡	Base model§		Base model§ + endoglin		
				OR (95% CI)	P ‡	OR (95% CI)	P ‡	
Preoperative PSA‖	1.06 (1.02-1.10)	0.001	75.1	1.04 (1.00-1.07)	0.02	1.05 (0.98-1.12)	0.15	
Clinical stage (T_2 vs T_1)	10.67 (2.35-48.32)	0.002	74.7	5.20 (1.07-25.31)	0.04	3.13 (0.26-37.23)	0.37	
Biopsy Gleason sum								
7 vs 2-6	8.15 (1.56-42.76)	0.01	82.8	4.82 (0.84-27.59)	0.08	10.95 (0.72-165.63)	0.08	
8-10 vs 2-6	40.18 (7.92-203.80)	<0.001		20.52 (3.82-110.07)	<0.001	18.57 (1.08-318.36)	0.04	
Test for trend	—	<0.001		—	0.001	—	0.13	
Endoglin‖	1.20 (1.12-1.29)	<0.001	95.6			1.17 (1.09-1.26)	<0.001	
Predictive accuracy (%) ‡				89.4		97.8		<0.001

Abbreviation: PA, predictive accuracy.
*P value comparing bias-corrected predictive accuracies is calculated with Mantel-Haenszel test.
†P values for ORs are calculated from logistic regression analysis.
‡Predictive accuracy was quantified as the area under the receiver operating characteristic curve and was bias corrected with 200 bootstrap resamples in the multivariable analyses.
§Base model = predictive model including preoperative total PSA, clinical stage, and biopsy Gleason sum.
‖Preoperative PSA and endoglin were modeled as continuous variables.

preoperative model (including total PSA, clinical stage, and biopsy Gleason sum) significantly improved its predictive accuracy from 89.4% to 97.8% ($P < 0.001$).

Figure 3A shows the nomogram for prediction of lymph node metastasis based on preoperative plasma endoglin and standard preoperative predictors. The calibration plot is shown in Fig. 3B. Assessment of the nomogram axes indicates that plasma endoglin contributes the highest number of risk points when all other variables are held constant.

Discussion

Conventional imaging modalities used for clinical staging in prostate cancer (2) are inadequate to detect small but clinically significant lymph node metastases. Currently, preoperative predictive models that incorporate preoperative serum total PSA, biopsy Gleason sum, and clinical stage are used to estimate the risk of lymph node metastases (18–22), but their predictive accuracies are not perfect, ranging from 76% to 89% (18–22) depending on the study population, incidence of positive lymph nodes, and variability in surgical technique. Although it is recognized that pelvic lymphadenectomy can provide important staging and prognostic information, it is still not clear in whom this procedure should be done (23). Doing pelvic lymphadenectomy on all patients is not universally practiced, as this procedure could be time consuming and is not without morbidity (24). Moreover, pelvic lymphadenectomy is not routinely done with pure and robot-assisted laparoscopic prostatectomy. As such, it would be of tremendous benefit to have an accurate blood marker that identifies patients in whom pelvic lymphadenectomy should be done.

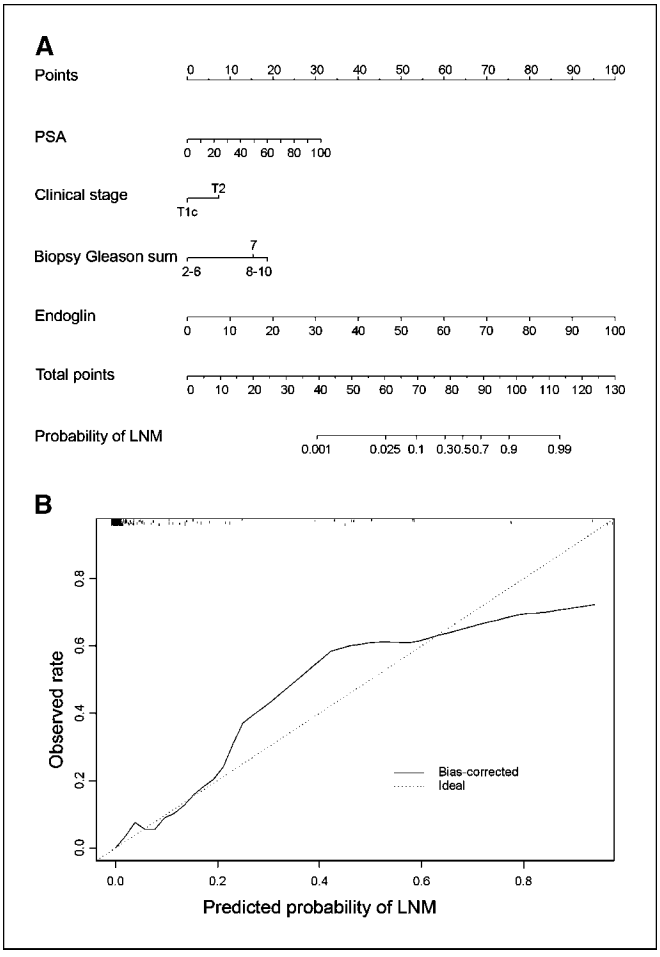

Fig. 3. *A,* nomogram for prediction of lymph node metastasis. Instructions for nomogram use: locate patient values at each axis. Draw a vertical line to the "Points" axis to determine how many points are attributed for each variable value. Sum the points for all variables. Locate the sum on the "Total points" line. Draw a vertical line toward the "Probability of LNM" to determine the probability of lymph node metastasis at radical prostatectomy. LNM, lymph node metastasis. *B,* calibration plot depicting performance of the nomogram. *X* axis, nomogram-predicted probability of lymph node metastasis; *Y* axis, actual proportion of lymph node metastasis detected during radical prostatectomy. Interrupted diagonal line, performance of an ideal nomogram in which predicted and actual probabilities are identical; solid line, bias-corrected estimates of accuracy.

Using multivariable analysis, we found that preoperative plasma endoglin level was the strongest predictor of lymph node metastasis in patients with clinically localized prostate cancer. The addition of endoglin to standard preoperative variables improved the ability to predict lymph node metastasis by a statistically and clinically significant margin. In addition, preoperative plasma endoglin levels were associated with markers of biologically aggressive prostate cancer, such as positive surgical margins, higher pathologic Gleason sum, and higher serum total PSA levels. We have developed and internally validated a preoperative nomogram with an improved predictive accuracy of 97.8%, using plasma endoglin level, in addition to routinely measured variables, such as total PSA, clinical stage, and biopsy Gleason sum. This tool can be used by clinicians to more accurately estimate the probability of lymph node metastasis in patients with clinically localized prostate cancer and subsequently counsel their patients whether they should undergo pelvic lymphadenectomy or not.

Increased endoglin has been reported in the plasma of patients with metastatic colon and breast cancers (11, 12, 25). Findings from these studies suggest that plasma endoglin levels could be used to identify early metastases (11, 12). The exact source and biological role of elevated levels of plasma endoglin is not clearly defined though (26). Endoglin expression is restricted to endothelial cells and is not present in the tumor cells themselves (9). However, it is possible that growth factors released by tumor cells, such as TGF-β1, could cause an increase in endoglin expression (27). This could be an important mechanism in prostate cancer progression and metastasis, where plasma TGF-β1 is elevated, especially in patients with nodal and bone metastasis (28, 29). Knowing that betaglycan, a TGF-β coreceptor with partial sequence identity to endoglin, can be released from tissues by membrane-type metalloproteinase-1 (30), it is possible that endoglin is being released through a comparable mechanism (26).

Use of preoperative plasma endoglin could help identify patients at risk for lymph nodes metastasis who should undergo pelvic lymphadenectomy. In addition, it may spare patients at low risk of lymph node metastasis the potential morbidity of an unnecessary lymphadenectomy. Further research is necessary to elucidate the role of endoglin as a surrogate marker for development of new blood vessels in prostate cancer metastases, thus facilitating the assessment of the response to angiogenesis inhibitors.

Some limitations of this study should be noted. First and foremost are the limitations inherent to any retrospective study. Second, the sample size and small number of events may have limited our ability to detect small differences attributed to other variables. Larger prospective studies are needed to validate

endoglin as a blood marker for lymph node metastasis in patients with prostate cancer and to potentially build better preoperative predictive models of lymph node metastasis. Third, the standard lymph node sampling may have failed to detect all nodal metastases that could have been detected by a more extended lymphadenectomy (31, 32). Fourth, the predictive accuracy of the base model (without endoglin) was on the high end of the reported estimates in the literature (89%); this may in part due to the low number of detected lymph node metastasis in the current patient population.

Conclusion

Incorporation of preoperative plasma endoglin in a standard preoperative model improves its accuracy for prediction of lymph node metastases in patients with clinically localized prostate cancer by a statistically and clinically significant margin. Larger multicenter prospective studies are needed to validate these findings before the clinical use of endoglin as a marker for predicting lymph node metastasis in patients with clinically localized prostate cancer.

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