A novel tool to predict lymph node metastasis in patients with prostate cancer based on clinical and ^{68}Ga-PSMA PET/CT parameters

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ABSTRACT

INTRODUCTION: We sought to develop a model that predicts lymph node invasion (LNI) in patients with intermediate- and high-risk prostate cancer incorporating preoperative clinical and ^{68}Ga-prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) parameters.

METHODS: A cohort of 413 consecutive patients diagnosed with prostate cancer who underwent ^{68}Ga-PSMA PET/CT prior to radical prostatectomy from 2015–2020 was used to develop and validate the model. The cohort was split into a learning (70%) and a validation group (30%). The former was used to identify clinical and ^{68}Ga-PSMA PET/CT parameters (number and diameter of PET-positive lymph nodes) for prediction of pathologic LNI by applying multivariable logistic regression analyses. The discrimination ability of the model was evaluated using the area under the receiver operating characteristic (ROC) curve and internal validation was performed using the validation cohort.

RESULTS: One-hundred sixty-three men (39%) were categorized as high-risk, 168 (41%) as unfavorable-intermediate-risk, and 82 (20%) as favorable-intermediate-risk. Thirty-one patients (7.5%) had LNI on final pathology. All underwent extended lymph node dissection. Clinical stage, the presence of PET-positive lymph nodes, and diameter of the largest PET-positive node were included in the final predictive model. Four different categories were defined for estimating the risk for LNI. Internal validation was completed after applying the four-tire classification on both the learning and validation groups and achieving similar results. The sensitivity, specificity, positive predictive value, and negative predictive value of the model were 97%, 54%, 15%, and 99%, respectively, and area under the ROC curve was 0.906 (95% confidence interval 0.83–0.95, p<0.001). Using a 5% cutoff as a threshold for performing lymph node dissection, only one patient with LNI on final pathology would have been classified erroneously as node negative, while 206 (50%) men would have been spared an unwarranted lymph node dissection.

CONCLUSIONS: We present a novel prediction model for LNI that incorporates clinical staging and molecular imaging data. Pending further validation, this model may improve the risk stratification and patient selection for lymph node dissection at time of radical prostatectomy.

INTRODUCTION

Pelvic lymph node dissection (PLND) is considered an essential diagnostic tool for nodal staging during radical prostatectomy.[1] In patients with positive lymph nodes, it may also offer a therapeutic benefit.[2] On the other hand, PLND may incur increased morbidity, prolonged hospitalization, and higher healthcare costs.[3,4] Current European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) prostate cancer guidelines recommend PLND in patients with an estimated risk for positive lymph nodes exceeding 5% and 2%, respectively, as calculated by nomograms incorporating clinical preoperative information.[5] Contemporary nomograms have demonstrated consistently good predictive accuracy.[6-9] Yet, according to the NCCN risk stratification scheme, almost every patient with high-risk or unfavorable-intermediate-risk prostate cancer should undergo PLND, whereas only 10–15% of these patients will ultimately have lymph node invasion (LNI) on final pathology.[10,11]

^{68}Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) is a promising, novel tool shown to be superior over conventional imaging modalities for staging patients with newly diagnosed prostate cancer. Several studies, mostly applying small cohorts, evaluated the specificity and sensitivity of ^{68}Ga-PSMA PET/CT in detecting LNI prior to radical prostatectomy,[12-17] concluding it might add valuable information and provide a more

KEY MESSAGES

- ^{68}Ga-PSMA (PET/CT) is a novel tool shown to be superior to conventional imaging modalities for staging patients with newly diagnosed prostate cancer.
- We developed a model that predicts lymph node invasion in patients with intermediate- and high-risk prostate cancer incorporating preoperative clinical and ^{68}Ga-PSMA PET/CT parameters.
- Four different categories were defined for estimating the risk for lymph node invasion.
- Risk group 4 (PET-positive pelvic nodes >6 mm OR clinical stage T3 and PET-positive pelvic nodes ≤6 mm) had 100% risk for pathologic lymph node invasion.

accurate loco-regional staging to improve the selection of patients who may benefit from PLND during radical prostatectomy.

In the current study, we evaluated the accuracy of ^{68}Ga-PSMA PET/CT in detecting LNI among patients with intermediate- and high-risk prostate cancer undergoing radical prostatectomy. We also sought to develop a novel predictive model based on clinical and pre-prostatectomy ^{68}Ga-PSMA PET/CT staging data to enhance the prediction of LNI in this setting, thus identifying the appropriate candidates for PLND.

METHODS

After obtaining institutional review board approval, we retrospectively analyzed a prospectively maintained, single-institution database of 422 consecutive men with biopsy-proven intermediate-/high-risk prostate cancer who underwent ^{68}Ga-PSMA PET/CT prior to robotic-assisted laparoscopic radical prostatectomy (RALRP) and extended PLND, namely the common iliac, hypogastric, external iliac, and obturator lymph nodes bilaterally. Nine patients were excluded due to lack of ^{68}Ga uptake within the prostate, leaving a total of 413 men for further analyses. Preoperative clinical characteristics were collected, including prostate-specific antigen (PSA) levels, clinical stage and biopsy data (Gleason grade group [GG]), number of cores taken, and number of positive cores. Gleason grading was defined accord-

Table 1. Patients' characteristics (N=413)

Age (years), median (IQR)	67 (62–71)
PSA (ng/ml), median (IQR)	8 (6–12.6)
Biopsy Gleason grade, n (%)	
1	18 (4%)
2	161 (39%)
3	116 (28%)
4	83 (20%)
5	35 (9%)
Positive cores, median (IQR)	0.33 (0.25–0.5)
Clinical stage, n (%)	
T1	221 (54%)
T2	158 (38%)
T3	34 (8%)
Risk group, n (%)	
Favorable intermediate	82 (20%)
Unfavorable intermediate	168 (41%)
High risk	163 (39%)
Total patients with PET-positive lymph nodes, n (%)	31 (8%)
Short axis diameter of PET-positive node (mm), median (IQR)	8 (5–11)
Pathologic Gleason grade, n (%)	
1	10 (2%)
2	149 (36%)
3	184 (45%)
4	26 (6%)
5	44 (11%)
Pathologic stage, n (%)	
T2	149 (36%)
T3a	182 (44%)
T3b	82 (20%)
Number of lymph nodes, median (IQR)	14 (11–18)
Lymph node invasion, n (%)	31 (8%)
Positive surgical margins, n (%)	70 (17%)

IQR: interquartile range; PET: positron emission tomography; PSA: prostate-specific antigen.

ing to the International Society of Urological Pathology (ISUP) 2014 consensus classification.[18]

PET technique and analysis

^{68}Ga-PSMA was used as the PSMA ligand. PET images were reconstructed by means of an ordered-subsets expectation maximization algorithm. CT data were used for attenuation correction. Images were reported by high-volume dedicated nuclear medicine readers. Lesions with increased tracer uptake above background were considered positive. Readers also reported the number of pelvic nodes with high PSMA uptake and the short axis diameter (SAD) of the largest PET-positive lymph node.

Histopathologic evaluation

Surgical specimens were evaluated by dedicated uropathologists using a predetermined protocol in accordance with the 2014 ISUP Consensus conference guidelines. The pelvic lymph nodes and associated fat were paraffin embedded and dissected meticulously. The total lymph node count and number of positive nodes (including palpable and microscopically identifiable) were recorded.

Statistical analysis

The primary endpoint was defined as the presence of pathologically proven LNI. Categorical variables were presented as proportions, and continuous variables were evaluated for normal distribution and reported as median and interquartile range (IQR). We randomly stratified the study cohort into two subgroups: a learning subset (70%) and a validation subset (30%).

The groups were compared and matched using the Chi-squared and Mann Whitney tests. Logistic regression applying a forward method was used to devise the prediction model using the learning subset. Classification methods (Chi-squared automatic interaction detection [CHAID] and classification and regression tree [CART]) were applied to identify threshold values. Likelihood ratio was used as criteria for inclusion ($p<0.05$).

The discrimination ability of the model was evaluated using the area under the receiver operating characteristic (ROC) curve. The model was set to achieve high sensitivity and hence high negative predictive value (NPV). The performance of the tool was evaluated using the validation group. Sensitivity, specificity, positive predictive value (PPV), NPV, positive likelihood ratio, and negative likelihood ratio were reported for the learning group, validation group, and the entire cohort. All statistical tests were performed using SPSS 27 (IBM Corp. Armonk, NY, U.S.) and NCSS 2020 (Kaysville, UT, U.S.).

Table 2. Characteristics of patients in the learning and validation groups

Predictor	All cohort (N=413)	Learning group (n=295)	Validation group (n=118)	p
Age (years), median (IQR)	68 (62–71)	68 (63–71)	67 (62–70)	0.193
Core ratio (%), median (IQR)	33 (25–50)	33 (25–50)	33 (25–50)	0.544
Gleason grade, median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.581
PSA (ng/ml), median (IQR)	8 (6–12.6)	8.1 (5.8–12)	8 (6–13)	0.358
Short axis diameter of PET-positive node (mm), median (range)	0 (0–16)	0 (0–16)	0 (0–14)	0.578
Risk group				0.724
Favorable-intermediate	107 (26.0%)	78 (27%)	29 (25%)	
Unfavorable-intermediate	143 (34.7%)	104 (35%)	39 (33%)	
High	162 (39.3%)	112 (38%)	50 (42%)	
Clinical stage				0.492
1	220 (54%)	152 (52%)	68 (57%)	
2	158 (38%)	118 (40%)	40 (35%)	
3	34 (8%)	24 (8%)	10 (8%)	
PET-positive lymph nodes	31 (7%)	21 (7%)	10 (8%)	0.643
Number of PET-positive lymph nodes, median (range)	0 (0–4)	0 (0–5)	0 (0–4)	0.558
Pathologic LNI	31 (8%)	23 (8%)	8 (7%)	0.717

IQR: interquartile range; LNI: lymph node invasion; PET: positron emission tomography; PSA: prostate-specific antigen.

RESULTS

Patient characteristics

A total of 413 men at a median age of 67 years (IQR 62, 71) were included in the study cohort; 250 patients (61%) were categorized as intermediate-risk and 163 (39%) were considered high-risk based on the NCCN risk group stratification. Thirty-one patients (7.5%) had PET-positive lymph nodes on preoperative imaging. Thirty-one patients (7.5%) had LNI on final pathology. The median number of retrieved lymph nodes was 14 (IQR 11–18). Clinical and pathologic characteristic of the study cohort are summarized in Table 1.

Table 3. Univariable analyses identifying preliminary independent predictors of LNI

Predictor	No (n=271)	Yes (n=23)	p
Age (years)	68 (63–71)	67 (58–70)	0.249
Core ratio (%)	33 (25–50)	50 (33–83)	0.008
Gleason grade	3 (2–4)	3 (2–4)	0.025
PSA (ng/ml)	8 (5.7–11.5)	12.5 (6.5–20)	0.015
Short axis diameter of PET-positive lymph node (mm)	0 (0–0)	8 (0–11)	<0.001
Risk group			0.006
Favorable-intermediate	77 (28.4%)	1 (4.4%)	
Unfavorable-intermediate	97 (35.8%)	7 (30.4%)	
High	97 (35.8%)	15 (65.2%)	
Clinical stage			0.001
1	147 (54.2%)	5 (21.7%)	
2	106 (39.1%)	12 (52.2%)	
3	18 (6.7%)	6 (26.1%)	
PET-positive lymph nodes	6 (2.2%)	15 (65.2%)	<0.001
Number of PET-positive lymph nodes	0 (0–0)	1 (0–2)	<0.001

LNI: lymph node invasion; PET: positron emission tomography; PSA: prostate-specific antigen.

Model construction and internal validation

There were no significant differences in clinical or pathologic variables between the learning and validation groups (Table 2). Using classification methods in the learning group, we identified threshold values for each variable. Table 3 demonstrates the crude association between each variable and the presence of LNI. Clinical stage, ^{68}Ga-PSMA uptake in the pelvic nodes, and SAD of the largest PET-positive lymph node were included in the final logistic regression model. Based on this model, four different categories of the risk of LNI were defined (Figure 1):

- Risk group 1 (clinical stage T1 and PET-negative pelvic nodes): 0% risk for LNI
- Risk group 2 (clinical stage T2 and PET-negative pelvic nodes): 5.5% risk for LNI
- Risk group 3 (clinical stage T3 and PET-negative pelvic nodes OR clinical stage T1 or T2 and PET-positive pelvic nodes ≤6 mm): 11.1% risk for LNI
- Risk group 4 (any clinical stage and PET-positive pelvic nodes >6 mm OR clinical stage T3 and PET-positive pelvic nodes ≤6 mm): 100% risk for LNI
- The area under the ROC curve for this model was 0.9484 (95% confidence interval [CI] 0.8693–0.9801, p<0.001) (Figure 2). To achieve high sensitivity and NPV, we defined a cutoff threshold of 5%. Internal validation was carried out by applying this classification scheme on both the learning and validation groups, achieving similar results (Table 4).

Clinical use

The sensitivity of the entire cohort using a threshold of 5% for defining LNI was 97% (95% CI 83.3–99.9%), specificity was 54% (95% CI 48.1–59.2%), PPV of 15% (10.1–20.2%), NPV of 99.5% (97.3–100%), positive likelihood ratio of 2.11 (1.86–2.39), and negative likelihood ratio of 0.06 (0.01–0.41). The area under the ROC curve for our prediction model in the entire cohort was 0.906 (95% CI 82.7–95%, p<0.001). When using the 5% cutoff, only one patient with LNI in the entire cohort would have been classified erroneously as node-negative, whereas 206 (50%) of the men would potentially be spared an unwarranted PLND. A decision-making tree using our model is presented in Figure 3.

DISCUSSION

We developed and validated a preoperative tool for predicting LNI in patients with intermediate- and high-risk prostate cancer. Our model was able to stratify the risk of LNI accurately based on three distinct parameters: clinical stage, the presence of positive pelvic nodes on PET imaging, and the SAD of the largest PET-positive node.

Accurate staging of prostate cancer, particularly in the high-risk setting, remains a challenge. Among patients diagnosed with high- or intermediate-risk disease, current guidelines recommend preoperative staging using CT/magnetic resonance imaging (MRI) and bone scan.[5,19] These modalities are relatively insensitive in diagnosing LNI.

^{68}Ga-PSMA PET/CT has gained an increasing role in evaluation of men with biochemical failure and most studies focused on assessment of metastatic and recurrent disease.[20,21] Evidence regarding its utility in loco-regional staging of naive patients, and particularly assessment of LNI, are scarce. The largest study to date evaluated 198 men who underwent ^{68}Ga-PSMA PET/CT prior to RALRP and showed PPV and NPV of 67.7% and 80.8%, respectively.[13]

The proPSMA trial, a prospective, randomized trial in patients with high-risk prostate cancer, explored the

diagnostic utility of ^{68}Ga-PSMA PET/CT as an alternative to conventional imaging. In that trial, ^{68}Ga-PSMA PET/CT had a higher sensitivity (85% vs. 38%) and specificity (98% vs. 91%), which translated into a 92% vs. 65% accuracy in detecting both pelvic nodal involvement and distant metastases favoring ^{68}Ga-PSMA PET/CT over conventional imaging modalities.[17]

American Urological Association (AUA) guidelines recommend PLND in every man with unfavorable-intermediate or high-risk prostate cancer.[19] The EAU and NCCN guidelines recommend the use of predictive models to help identify patients with high probability of LNI and various cutoffs for selecting the appropriate candidates for PLND.[5,10] Commonly used tools to assess the risk of LNI include the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram[9] and the Partin table,[8] which use preoperative PSA, clinical stage, and biopsy Gleason score. These tools are based on clinical and laboratory data and while generally exhibit good performance, they recommend that almost every patient with high-risk and unfavorable-intermediate-risk prostate cancer should undergo PLND.

The updated 2018 Briganti nomogram has further incorporated MRI findings to enhance the predicting ability of LNI in prostate cancer patients.[7] In a contemporary series of 12 000 men who underwent radical prostatectomy and PLND, the performance characteristics of the MSKCC, Partin, and updated Briganti nomograms for prediction of LNI were compared. The area under the ROC curve was 0.79, 0.78, and 0.76, respectively, with the former two models underestimating and the latter overestimating the risk of LNI. PLND-related morbidity (lymphocele, lymphedema, hemorrhage, infection, and sepsis) was encountered in 9% of the patients.[22] With that in mind, it would seem reasonable to incorporate preoperative PET-PSMA findings with well-established clinical characteristics to allow for more accurate preoperative planning.

Our study demonstrates that a simple prediction model based on the clinical stage, presence of PET-positive nodes, and their SAD is highly successful in predicting the individual risk of LNI. As aforementioned, setting the bar at 5% (i.e., a 5% or higher risk of LNI) to achieve the highest possible sensitivity and NPV at the potential disadvantage of reduced specificity would still allow us to avoid 50% of unnecessary PLNDs. Because microscopic LNI might be detected in many normal-appearing (<1 cm) nodes, the SAD alone has been proven limited by means of other imaging modalities.[23] Our model, however, shows that in PET-positive nodes, a SAD <6 mm is an important predictor of LNI.

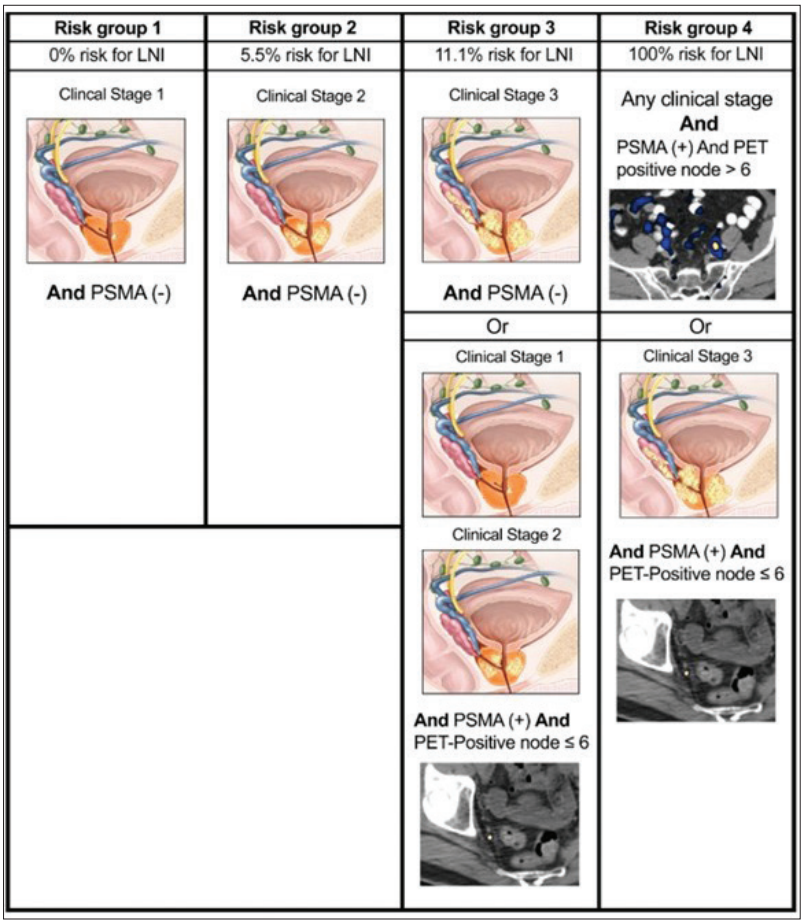

Figure 1. Four different risk categories for lymph node invasion (LNI), based on the predicting model. PET: positron emission tomography; PSMA: prostate-specific membrane antigen.

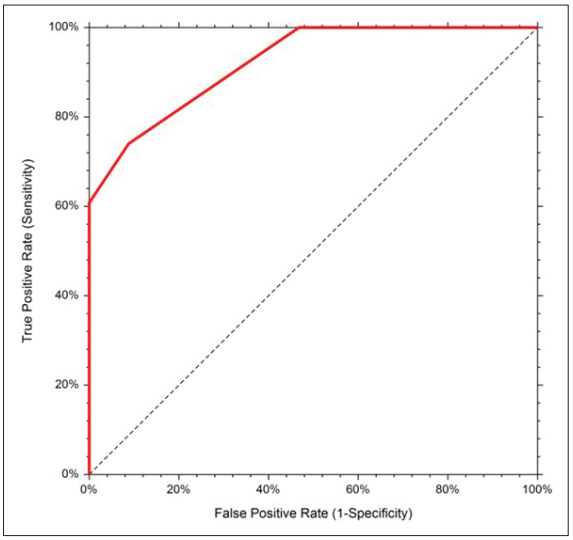

Figure 2. Receiver operating characteristic curve for the predicting model, area under the curve was 0.9484 (95% confidence interval 0.8693, 0.9801, p<0.001).

Table 4. Prediction model applied on both the learning and validation groups

	Learning group	Validation group
Sensitivity	100% (95% CI 85.2–100)	87.5% (95% CI 47.4–99.7)
Specificity	53.1% (95% CI 45–59.2)	56.4% (95% CI 46.6–65.8)
PPV	15.3% (10–22.1)	12.7% (5.3–24.5)
NPV	100% (97.5–100)	98.4% (91.5–100)
LR+	2.14 (1.88–2.42)	2.01 (1.43–2.81)
LR-	0.04 (0–0.64)	0.22 (0.04–1.40)

CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NPV: negative predictive value; PPV: positive predictive value.

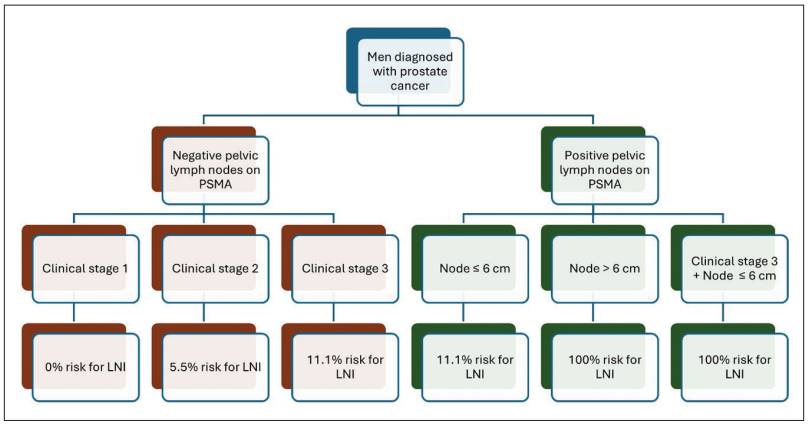

Figure 3. A decision-making tree using the predicting model. LNI: lymph node invasion; PSMA: prostate-specific membrane antigen.

While the role of digital rectal examination (DRE) in screening of prostate cancer remains debatable,[24] its importance in clinical staging as an independent predictor for LNI and adverse pathology after treatment is well-established.[10,25] Our model reiterates its value as an independent predictor of LNI even in an era of advanced, state-of-the-art imaging modalities. Other independent predictors of outcome, such as preoperative PSA and biopsy Gleason score, did not improve the performance of our LNI prediction tool. Others have also demonstrated that once prostate cancer cohorts are restricted to high-risk patients, PSA and biopsy Gleason score may become less useful in predicting LNI.[26,27]

Limitations

Some limitations of our study should be noted. First, a PET-positive finding may occasionally be interpreted as equivocal. While only dedicated and highly experienced nuclear medicine specialists unaware of the final pathology data were involved in our study, some of their readings might have been biased. Second, while our model was validated internally, further external validation must be conducted in order to corroborate our results. Third, while the extent of lymph node dissection, and hence accuracy, of pathologic nodal staging may not be uniform among all surgeons, the high median number of retrieved lymph nodes likely reflects an adequate dissection performed in most cases. And lastly, the low prevalence of LNI in our cohort may impose problems in creating a validated model; however, our results demonstrated that this model is valid.

CONCLUSIONS

This study presents a novel prediction tool that incorporates both clinical staging and molecular imaging data and can be used conveniently to facilitate the preoperative prediction of LNI in patients with high- and intermediate-risk prostate cancer. Both physicians and patients can exploit this model to evaluate the need for PLND, which stands in line with the current trend toward personalized medicine.[28,29]

COMPETING INTERESTS: The authors do not report any competing personal or financial interests related to this work.

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