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Prostate Cancer

Association Between Oncotype DX Genomic Prostate Score and Adverse Tumor Pathology After Radical Prostatectomy

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Article info

Abstract

Background: The Oncotype DX assay is a clinically validated 17-gene genomic assay that provides a genomic prostate score (GPS; scale 0–100) measuring the heterogeneous nature of prostate tumors. The test is performed on prostate tissue collected during biopsy. There is a lack of data on the association between the GPS and tumor pathology after radical prostatectomy (RP).

Objective: To investigate the association between GPS and final pathology, including extraprostatic extension (EPE), positive surgical margin (PSM), and seminal vesicle invasion (SVI).

Design, setting, and participants: Data for the 749 patients who underwent Oncotype DX assay and RP at a referral prostate cancer center between 2015 and 2019 were retrospectively assessed to evaluate the association between GPS and unfavorable pathology parameters.

Intervention: After a GPS genetic test, patients underwent robotic RP performed by the same surgeon.

Outcome measurements and statistical analysis: Multivariable logistic regression analyses were performed to assess the association between GPS and EPE, PSM, and SVI. The models were adjusted for age, clinical stage, prostate-specific antigen (PSA) level, Gleason score, and time between the genomic assay and surgery. The median time between Oncotype DX assay and surgery was 176 d (interquartile range [IQR] 141–226). The median age was 63 yr (IQR 58–68), median GPS was 29 (IQR 21–39), and median PSA was 5.7 ng/ml (IQR 4.6–7.7). In multivariable analyses assessing the odds ratio (OR) per 20-point change in GPS, GPS was an independent predictor of EPE (OR 1.8, 95% confidence interval [CI] 1.4–2.3) and SVI (OR 2.1, 95% CI 1.3–3.4). In addition, when patients were grouped by GPS quartile, the percentage of cases with EPE and SVI increased with the GPS quartile.

Conclusions: We provide evidence that the Oncotype DX GPS is significantly associated with adverse pathology after RP. Specifically, the risk of EPE and SVI increases with the GPS. Therefore, use of the Oncotype DX GPS may help clinicians to improve preoperative patient counseling and develop surgical strategies for patients with a higher chance of EPE or unfavorable pathological features.

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Patient summary: We studied whether the score for a prostate genetic test was associated with prostate cancer pathology findings for patients who had their prostate removed. We found that the risk of prostate cancer spread outside the gland and to the seminal vesicle increases with higher test scores. These findings may help surgeons in counseling patients on surgical options for prostate cancer.

1. Introduction

Prostate cancer (PCa) is currently the second leading cause of cancer-related death among men in the USA, reaching close to 30 000 deaths per year. Current methods for assessing PCa at diagnosis include digital rectal examination, TNM staging, Gleason score, and measurement of serum prostate-specific antigen (PSA) [1–4]. However, because of growing concerns regarding the reliability of these traditional measures and increasing rates of high-risk cancers [5], the use of genomic tests has recently been introduced to enhance understanding of the heterogeneous nature of tumors.

Oncotype DX is a multigene expression assay that produces a genomic prostate score (GPS) according to gene expression in an individual tumor [6,7]. The test evaluates the presence of 17 different genes (12 genes associated with aggressive cancer and 5 reference genes) in order to create a GPS score, which ranges from 0 to 100 [7]. This test is performed on tissue samples collected during prostate biopsy and clinical validation has confirmed that it can predict the probability of adverse pathology, cancer-related death, and metastasis within 10 yr [7]. Unlike traditional biopsy core sampling, which can only provide information on tumor within the biopsy cores, the Oncotype DX assay can account for the entire genomic make-up of a tumor.

However, there is a lack of data on the ability of Oncotype DX to predict final tumor pathology features such as extraprostatic extension (EPE), positive surgical margin (PSM), and seminal vesicle invasion (SVI). Using data from the largest single-center cohort of patients who underwent radical prostatectomy (RP) and genomic testing, we evaluated the association between the Oncotype DX GPS and final pathology in terms of EPE, SVI, and PSM.

2. Patients and methods

We performed a retrospective analysis of 749 patients who underwent Oncotype DX genomic testing before RP from February 2015 until December 2019 at a prostate cancer referral center (AdventHealth Global Robotics Institute, Celebration, FL, USA). The final pathology examinations were conducted by a single uropathologist with more than 10 yr of expertise in PCa to ensure consistency among the evaluations.

Three multivariable logistic regression analyses were conducted to evaluate associations between the Oncotype DX GPS and pathology features at RP (EPE, SVI, and PSM). The covariates included were patient age, clinical stage, PSA level, biopsy Gleason score, and time between the genomic assay and surgery. The variables were selected on the basis of literature reports suggesting their association with the endpoint characteristics [8]. These variables are also those included in the Memorial Sloan Kettering Cancer Center nomogram, which is currently used as a common predictor for EPE, PSM, and lymph node invasion (LNI) [9–11]. LNI was not evaluated in the study as a very restricted number of patients were positive for LNI.

We tested the hypothesis of equal GPS distributions in the groups with and without EPE, SVI, and PSM using the Wilcoxon rank-sum test. The odds ratio (OR) was then calculated for each characteristic on final tumor pathology (EPE, SVI, PSM) per 20-point change in GPS with GPS as a continuous variable. The decision to assess ORs per 20-point change in GPS was made according to previous validation studies on the GPS and previous studies that associated the GPS with adverse pathology [6,7,12]. In addition, patients were divided into GPS quartiles and the ORs for each quartile group were adjusted for the same covariates. The area under the receiver operating characteristic curve (AUC) for models with and without GPS (nested logistic models) were compared following the approach suggested by Demler et al [13]. The test of association was only performed for inclusion of the GPS (a Wald test on the GPS coefficient in logistic regression). If the result was statistically significant, the change in AUC was estimated with a confidence interval according to the DeLong approach. Finally, in order to assess for potential overfitting of our logistic regression, cross-validation was performed by assessing the difference between in-sample and out-of-sample gains in the AUC for each model.

The median and interquartile range (IQR) are reported for continuous variables, and the frequency and proportion for categorical variables. Two-tailed tests with $p < 0.05$ were considered statistically significant. Statistical analyses were performed using Stata 16 (StataCorp, College Station, TX, USA) and R v4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) software.

3. Results

3.1. Study population

Table 1 lists descriptive characteristics for the study cohort. The median time between the Oncotype DX assay and surgery was 176 d (IQR 141–226). The median age was 63 yr (IQR 58–68), and the median Oncotype DX GPS was 29 (IQR 21–39). There were no patients with a GPS higher than 74. The median PSA level was 5.7 ng/ml (IQR 4.6–6.6). Overall, 226 patients (30.2%) had International Society of Urological Pathology grade group 1, 419 (55.9%) had grade group 2, 97 (12.9%) had grade group 3, six (0.8%) had grade group 4, and one (0.1%) had grade group 5 PCa. The median percentage of cores involved on biopsy was 31.6% (IQR 16.7–46.2%). The median follow-up was 22 mo (IQR 16–29).

3.2. Association between GPS and tumor pathology

Within our cohort, the 248 patients (33%) with EPE (Table 2) had a median GPS of 34 (IQR 24–44), while the 502 patients (67%) without EPE had a median GPS of 27 (IQR 19–35). The median GPS difference between patients who were positive and negative for EPE was 7 points (95% confidence interval [CI] 5–9; $p < 0.001$).

Table 1 – Preoperative characteristics and covariates included in the logistic regression analysis

Parameter	Result
Median age, yr (interquartile range)	63 (58–68)
Age category, *n* (%)	
<55 yr	100 (13.3)
55–65 yr	315 (42.1)
>65 yr	334 (45.6)
Median prostate-specific antigen, ng/ml (interquartile range)	5.7 (4.6–7.7)
Prostate-specific antigen category, *n* (%)	
<4 ng/ml	100 (13.3)
4–9.99 ng/ml	554 (74)
10–19.99 ng/ml	90 (12)
≥20 ng/ml	5 (0.7)
International Society of Urological Pathology grade group, *n* (%)	
Grade group 1	226 (30.2)
Grade group 2	419 (55.9)
Grade group 3	97 (12.9)
Grade group 4	6 (0.8)
Grade group 5	1 (0.1)
Clinical stage, *n* (%)	
T1a	2 (0.3)
T1c	595 (79.1)
T2a	40 (5.3)
T2b	5 (0.7)
T2c	2 (0.1)
Tx	105 (14.4)
Median GPS (interquartile range)	29 (21–39)
Median time between GPS test and surgery, d (interquartile range)	179 (141–226)
GPS = genomic prostate score.	

The 40 patients (5%) with SVI had a median GPS of 38 (IQR 29–49) compared to median GPS of 28 (IQR 20–38) among the 709 patients who did not have SVI. The median GPS difference between patients with and without SVI was 10 points (95% CI 5–14; $p < 0.001$).

The 140 patients (18.7%) with PSM had a median GPS of 29 (IQR 23–41), while the patients without PSM had a median GPS of 28 (IQR 20–38). The median GPS difference between patients with and without PSM was 2 points (95% CI 0–5; $p = 0.049$). When patients were grouped by GPS quartile, the percentage of patients with EPE and SVI increased with increasing quartile (Fig. 1).

When evaluated as a continuous variable, the GPS (per 20-point increase) showed ORs >1 for EPE and SVI (Fig. 2). Specifically, GPS was an independent predictor of EPE (OR 1.8, 95% CI 1.4–2.3) and SVI (OR 2.1, 95% CI 1.3–3.4). The results are presented in Table 3.

Table 4 presents ORs for the GPS quartiles, taking the first GPS quartile as the reference. Patients in quartiles 3 and 4 (GPS ≥29) had significantly higher odds of EPE and SVI, confirming the association between the Oncotype DX GPS and final tumor pathology.

Finally, inclusion of GPS as a continuous variable in logistic regression models led to a significant increase in predictive value for EPE (AUC 0.68 vs 0.70; Fig. 3) and SVI (AUC 0.74 vs 0.78; Fig. 4), but not for PSM (AUC 0.62 vs 0.62; Fig. 5). Supplementary Table 3 presents out-of-sample (cross-validated) AUCs showing that the increase in in-sample AUC (0.777 − 0.744 = 0.033) was almost identical to the difference between the out-of-sample estimates (0.705 − 0.673 = 0.032). This means that the contribution of GPS to the prediction of SVI is not significantly affected by the (moderate) overfitting. ORs for the univariable and multivariable models are presented in Supplementary Tables 1 and 2.

4. Discussion

More than 11 validation studies involving >4500 patients have clinically demonstrated that the Oncotype DX GPS is a strong predictor of adverse pathology, metastasis at 10 yr, and PCa-related death [6,7,12]. Some authors have identified the GPS as a useful indicator when making clinical decisions between active surveillance and treatment for patients in low- and favorable intermediate-risk categories [6,14,15]. The test is also a strong predictor of biochemical recurrence in patients after RP [12]. However, there is a lack

Table 2 – Tumor pathology characteristics for the overall cohort and by GPS quartiles

| Characteristic	Patients, *n* (%)				
	Overall	GPS quartiles			
	(*n* = 749)	GPS 1–20	GPS 21–28	GPS 29–38	GPS ≥39
Extraprostatic extension	248 (33)	36 (20)	49 (27)	63 (33)	97 (51)
Seminal vesicle invasion	40 (5)	4 (2)	5 (3)	12 (6)	19 (10)
Positive surgical margin	140 (19)	27 (15)	34 (19)	35 (18)	44 (23)
Lymph node invasion	4 (0.5)	0 (0)	1 (0.1)	1 (0.1)	2 (0.3)
Tumor upgrading	378 (50)	93 (50)	89 (48)	90 (47)	106 (56)
Pathological stage					
T2	316 (42)	93 (50)	96 (52)	78 (41)	49 (26)
T2a	22 (3)	6 (3)	4 (2)	6 (3)	6 (3)
T2b	2 (0.3)	0 (0)	0 (0)	2 (1)	0 (0)
T2c	148 (20)	49 (26)	35 (19)	33 (17)	31 (16)
T3a	216 (29)	32 (17)	43 (23)	57 (30)	84 (44)
T3b	38 (5)	3 (2)	5 (3)	12 (6)	18 (10)
T4	7 (0.9)	2 (1)	2 (1)	2 (1)	1 (1)
GPS = genomic prostate score.					
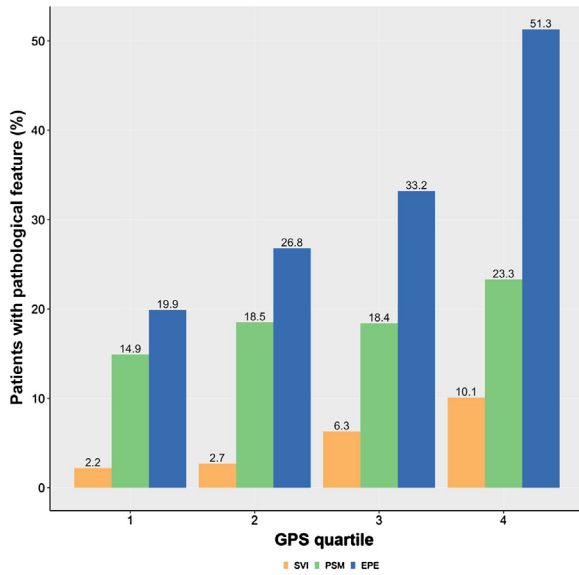
Fig. 1 – Patients were grouped into quartiles according to their genomic prostate score (GPS). The percentage of patients with extraprostatic extension (EPE) and seminal vesicle invasion (SVI) increases by GPS quartile, suggesting that the risk of EPE and SVI increases with patient GPS. PSM = positive surgical margin.

of data on association between the GPS and high-risk pathology features in patients who have undergone RP. Our study evaluated a cohort of 749 patients with low to high-grade PCa with data available for final pathology at RP

and preoperative GPS for prostate biopsy. To the best of our knowledge, this represents the first study to perform such an analysis.

Rocco et al [16] evaluated 19 different models used to predict EPE and concluded that most of the models are not reliable for EPE and may not be used for patient counseling. However, our study reported a novel correlation between GPS and final pathology, showing that the risk of EPE and SVI increases with the GPS. This independent association was strengthened by additional adjusted ORs revealing significant increases in the risk of EPE and SVI when the GPS was evaluated by quartiles and in continuous increments of 20 points. Moreover, the incremental gains in AUC on adding the GPS to models predicting EPE and SVI suggest that the GPS is not only independently associated with these high-risk features but also significantly improves our ability to predict their presence on final pathology. As age, PSA, clinical stage, and Gleason grade are all widely accepted predictors for EPE, SVI, and PSM, our comparison of the two multivariable models with and without the GPS shows that the GPS not only matches the predictive ability of established models but also adds to their cumulative ability to predict adverse final tumor pathology. While the increase in accuracy is not overwhelming, it reinforces our findings, namely that the Oncotype DX is a useful tool that can be combined with known predictors to improve preoperative patient counseling and assist in surgical planning for patients at higher risk of adverse pathological outcomes such as EPE.
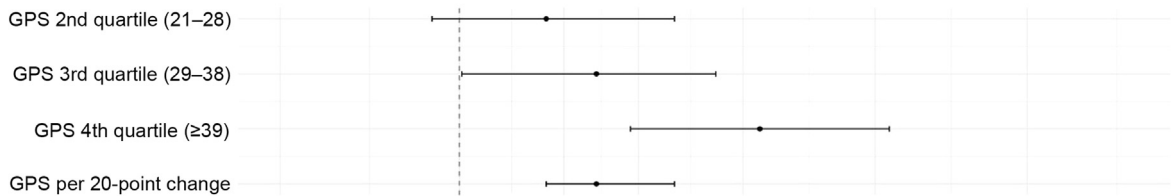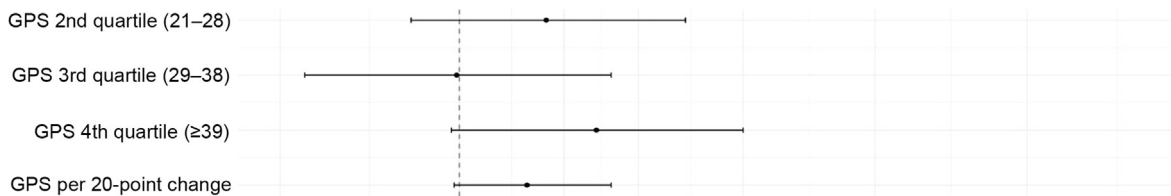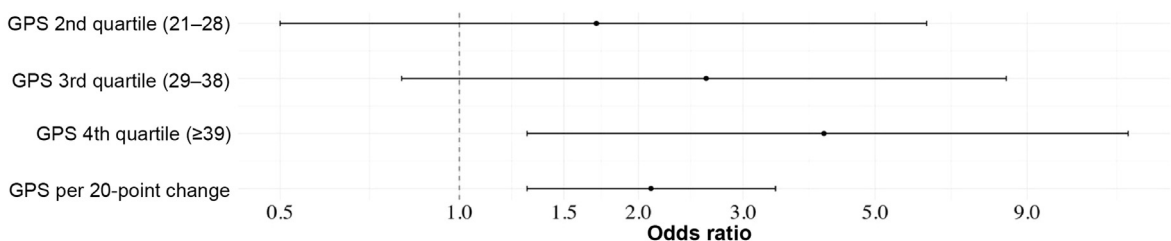

Fig. 2 – Odds ratios were calculated for each high-risk feature on final pathology for genomic prostate score (GPS) quartiles compared to the first quartile and for GPS as a continuous variable (per 20-point change). Patients in the third and fourth GPS quartile had a significantly higher risk of extraprostatic extension compared to those in the first quartile. Patients in the fourth GPS quartile had a significantly higher risk of seminal vesicle invasion) compared to those in the first quartile. Increments of 20 points in the GPS were significantly associated with a higher risk of EPE and SVI.

Table 3 – Odds ratio (adjusted for age, prostate-specific antigen level, clinical stage, Gleason score, and time between the genomic assay and surgery) for the presence of high-risk features on tumor pathology per 20-point change in Oncotype DX genomic prostate score

Characteristic	Odds ratio (95% CI)	p value [a]
Extraprostatic extension	1.8 (1.4–2.3)	<**0.001**
Seminal vesicle invasion	2.1 (1.3–3.4)	**0.004**
Positive surgical margin	1.3 (1.0–1.8)	0.06

CI = confidence interval.
[a] Values in bold are statistically significant.

Table 4 – Odds ratio (adjusted for age, prostate-specific antigen level, clinical stage, Gleason score, and time between the genomic assay and surgery) for the presence of high-risk features on tumor pathology by GPS quartile

GPS quartile	Odds ratio (95% confidence interval) [a]		
	EPE	SVI	PSM
Quartile 1 (GPS 0–20)	Reference	Reference	Reference
Quartile 2 (GPS 21–28)	1.4 (0.9–2.3)	1.7 (0.5–6.1)	1.4 (0.8–2.4)
Quartile 3 (GPS 29–38)	**1.7 (1.0–2.7)**	2.6 (0.8–8.6)	1.0 (0.6–1.8)
Quartile 4 (GPS ≥ 39)	**3.2 (1.9–5.3)**	**4.1 (1.3–13.3)**	1.7 (1.0–3.0)

GPS = genomic prostate score; EPE = extraprostatic extension; SVI = seminal vesicle invasion; PSM = positive surgical margin.
[a] Results in bold are statistically significant.

Fig. 4 – Receiver operating characteristic curves for multivariate models with and without the genomic prostate score (GPS) included for prediction of seminal vesicle invasion. The area under the curve (AUC) indicates the relative strength of prediction by each model. The model including GPS had significantly better AUC, indicating that inclusion of GPS in the multivariate model improved its ability to predict seminal vesicle invasion.

After evaluating 902 patients over median follow-up of 3 yr, Jayachandran et al [17] found that EPE, PSM, and SVI on final tumor pathology were related to prognosis after RP, including a higher probability of biochemical recurrence and higher path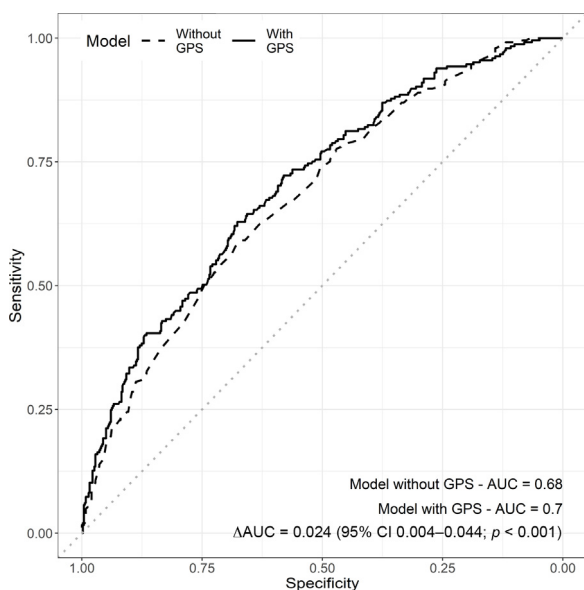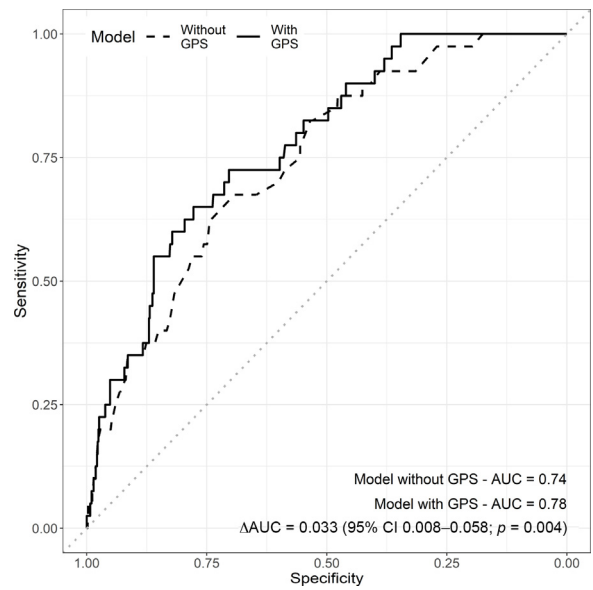ological stage. Therefore, in addition to assisting with preoperative patient counseling, knowledge of greater likelihood of EPE, SVI, and PSM may also be useful during key surgical steps such as nerve-sparing and apical dissection [18,19].

In this context, Caire et al [20] evaluating a cohort of 1895 patients who underwent RP and found that while
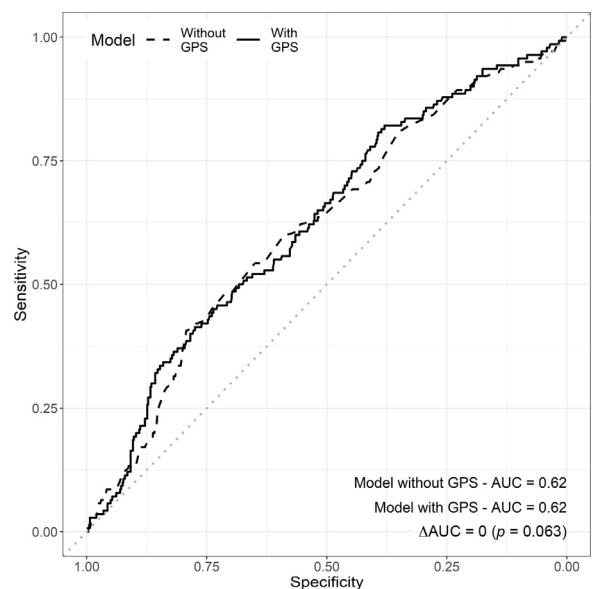

Fig. 3 – Receiver operating characteristic curves for multivariate models with and without the genomic prostate score (GPS) included for prediction of extraprostatic extension. The area under the curve (AUC) indicates the relative strength of prediction by each model. The model including GPS had significantly better AUC, indicating that inclusion of GPS in the multivariate model improved its ability to predict extraprostatic extension.

Fig. 5 – Receiver operating characteristic curves for multivariate models with and without the genomic prostate score (GPS) included for prediction of positive surgical margin. The area under the curve (AUC) indicates the relative strength of prediction by each model. The AUC for the two models is the same. Thus, inclusion of GPS did not improve the prediction of positive surgical margin by the multivariate model.

organ-confined disease was almost always removed via a nerve-sparing procedure with minimal rates of recurrence, surgeons may prefer to use a wider dissection plane for patients with a higher risk of EPE. Therefore, depending on the genomic make-up of the tumor, surgeons may consider taking greater precautions to avoid adverse pathology outcomes [20].

Knowing the tumor location (biopsy report/imaging examination) associated with a higher chance of EPE as suggested by the GPS may help during surgical planning and patient counseling. The higher chance of EPE at the prostate base and the middle of one side will interfere with the degree of nerve-sparing possible, because on that side the dissection needs to be wider than on the side without any lesion. Therefore, during preoperative consultation, knowing that the patient has a higher chance of EPE is helpful when explaining the surgical procedure and possible reduction in erection function due to lower preservation of the neurovascular bundle.

In addition, in academic centers in which residents and fellows perform surgery, knowing which side has a higher chance of EPE could change the surgical management because a more experienced surgeon can take over and dissect that side to optimize functional and oncological outcomes. In our study, GPS ≥29 points (quartiles 3 and 4) was associated with significantly higher OR for EPE (Table 4). Therefore, in our clinical practice we adopt a GPS of 29 as a threshold at which to perform more careful dissection on the tumor side.

Despite its strengths, our study is not devoid of limitations. First, the study is based on a retrospective analysis with all of its inherent limitations. Second, the median follow-up of 22 mo (IQR 16–29) is relatively short and does not allow us to evaluate stronger outcomes such as metastasis at 10 yr, biochemical recurrence, and PCa-related death. Future studies with long-term follow up are needed to overcome this issue. Third, the experience of our chief surgeon could be considered as a limitation regarding PSM rates. However, different centers worldwide with less experienced surgeons have described similar PSM rates to our data. We believe that the association between GPS and PSM will be valuable even in centers with less experienced surgeons. Finally, the number of SVI cases is below the minimum rate of one to ten (10 events for each predictive variable) and this could make our model vulnerable to overfitting. To ensure that the risk of overfitting was marginal, we conducted cross-validation comparisons of the increase in in-sample AUC and the increase in out-of-sample AUC. The AUC increases were almost identical for the in-sample and out-of-sample models, which means that the contribution of GPS to the prediction of SVI is not significantly affected by overfitting.

To the best of our knowledge, this is the largest cohort of patients both overall and of men with unfavorable intermediate and high risk who have undergone RP and Oncotype DX testing. In addition, this is the first study to describe an association between the GPS and tumor characteristics such as EPE and SVI. Understanding this association may be important for expanding the utility of the Oncotype DX to physicians who are planning to treat patients with potential tumor EPE.

5. Conclusions

We provided evidence that Oncotype DX GPS is significantly associated with adverse pathology after RP. Specifically, as the GPS increases, the risk of EPE and SVI also increases. Therefore, based on the GPS genetic test score of each patient, these findings may help clinicians to improve preoperative patient counseling and to perform surgical strategies in patients with higher chances of EPE or unfavorable pathological features.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euf.2021.03.015.

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