1-3-2021

External validation of genomic classifier-based risk-stratification tool to identify candidates for adjuvant radiation therapy in patients with prostate cancer

David I. Lee

Mohammed Shahait
Henry Ford Health

Deepansh Dalela

Jacob Keeley

Priti Lal

See next page for additional authors

Recommended Citation

Lee DI, Shahait M, Dalela D, Keeley J, Lal P, Vapiwala N, and Abdollah F. External validation of genomic classifier-based risk-stratification tool to identify candidates for adjuvant radiation therapy in patients with prostate cancer. World J Urol 2021.

Authors

David I. Lee, Mohammed Shahait, Deepansh Dalela, Jacob Keeley, Priti Lal, Neha Vapiwala, and Firas Abdollah

World Journal of Urology
https://doi.org/10.1007/s00345-020-03540-1

ORIGINAL ARTICLE

External validation of genomic classifier-based risk-stratification tool to identify candidates for adjuvant radiation therapy in patients with prostate cancer

David I. Lee[1] · Mohammed Shahait[2,3] · Deepansh Dalela[4] · Jacob Keeley[4] · Priti Lal[5] · Neha Vapiwala[6] · Firas Abdollah[7]

Received: 17 September 2020 / Accepted: 19 November 2020

Abstract

Objective To externally validate a Genomic Classifier (GC) based risk-stratification nomogram identifying candidates who would benefit from adjuvant radiation (aRT) therapy after radical prostatectomy (RP).

Methods We identified 350 patients who underwent RP, between 2013 and 2018, and had adverse pathological features (positive margin, and/or pT3a or higher) on final pathology. Genomic profile was available for all these men. The clinical recurrence-free survival was estimated using the Kaplan–Meier method. The external validity of the nomogram was tested using the concordance index (c-index), calibration plot, and decision curve analysis.

Results The median follow-up of the cohort was 26.5 months. Overall, 14% of the patients received aRT. During the follow-up period, 3.4% of the patients developed metastasis. Overall 3-year metastasis-free survival was 95% (95% CI 0.92–0.98). The c-index of the nomogram was 0.84. The calibration of the model was favorable. Decision-curve analysis showed a positive net benefit for probabilities ranging between 0.01 and 0.09, with the highest difference at threshold probability around 0.05. At that threshold, the net benefit is 0.06 for the model and 0 for treating all the patients.

Conclusion Our report is the first to confirm the validity of this genomic-based risk-stratification tool in identifying men who might benefit from aRT after RP. As such, it can be a useful instrument to be incorporated in shared decision making on whether administration of aRT will lead to a clinically meaningful benefit. Such a model can also be useful for patients' classification in future clinical trials.

Keywords Prostate cancer · Biomarkers · Radiation · Adjuvant · Radical prostatectomy

✉ Firas Abdollah
firas.abdollah@gmail.com

1 Department of Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA

2 Department of Surgery, King Hussein Cancer Center, Amman, Jordan

3 Vattikuti Urology Institute (VUI), Henry Ford Hospital, Detroit, USA

4 Department of Pathology, Perelman School of Medicine University of Pennsylvania, Philadelphia, USA

5 Department of Radiation Oncology, Perelman School of Medicine University of Pennsylvania, Philadelphia, USA

6 Wayne State University, Detroit, USA

7 VUI Center for Outcomes Research Analytics and Evaluation, Senior staff, Vattikuti Urology Institute (VUI), Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202-2689, USA

Introduction

In the past decade, the utilization of radical prostatectomy (RP) for high-risk and locally advanced prostate cancer has increased [1]. The risk of biochemical failure in this population ranges between 40 and 70%, which in turn increases the risk of metastasis and prostate cancer-specific mortality [2, 3]. Adjuvant radiation (aRT) improves progression-free survival, as well as overall survival in patients with locally advanced disease [4–8]. However, the number of patients needed to be treated to prevent prostate cancer-specific mortality is high, and aRT is associated with increased treatment-related toxicity and decreased quality-adjusted life expectancy [8]. Therefore, different prognostic nomograms were developed to optimize the post-operative management of prostate cancer patients. The majority of these tools relied on tumor histopathological features and various

Published online: 03 January 2021

prostate-specific antigen (PSA) measures and failed to account for molecular heterogeneity of prostate cancer [9].

Recently, a Genomic Classifier (GC)-based risk-stratification tool was proposed to identify candidates for aRT therapy after RP [10]. It was developed using a historical cohort of patients who underwent RP between 1990 and 2010. The nomogram estimates the probability of clinical recurrence (CR)-free survival after RP based on the following variables: pathologic stage ≥ T3b, pathologic Gleason score ≥ 8, pathological lymph node invasion (LNI), and GC score ≥ 0.6. To date, this nomogram has not been externally validated. This is a crucial piece of information, which allows for assessing the accuracy of the model outside of its original development cohort, which can shed light on its clinical utility. Moreover, the lack of external validation represents a limitation, as predictive models relying on historical data are not necessarily generalizable to contemporary patients, who can represent cohorts with different tumor burden, and possibly have access to more contemporary and different treatment options [11, 12]. Our study aimed to address this void and test the external validity of the aforementioned model in a contemporary cohort of men treated with robot-assisted RP at a single, high-volume, tertiary care center.

Material and methods

Study population

We included a total of 350 patients who underwent robot-assisted RP and bilateral pelvic lymph node dissection at a single, high-volume, tertiary medical center between 2013 and 2018 and were found to have adverse pathological features on their final pathology specimen (positive margin, and/or pT3a or higher), and reached undetectable PSA levels after surgery. Genomic profile data was obtained for all the patients. Data were prospectively collected in an institutional review board approved a comprehensive database. The decision and the timing to administer aRT therapy and androgen deprivation therapy were based on patient comorbidities and life expectancy, patients' treatment expectations, and consensus of our prostate cancer multidisciplinary team.

Covariates

The following variables were extracted for all patients: age at diagnosis (years), serum PSA value at diagnosis (ng/mL), pathological tumor stage (≤ pT2, pT3a,and pT3b) per AJCC 7th edition Classification [13], pathological Gleason score (≤ 6, 7(3 + 4, 4 + 3), 8, and 9–10), surgical margin status (negative or positive), pathological LNI status, receipt of aRT or salvage radiotherapy (sRT), and GC score.

Of note, aRT was defined as administering radiation at PSA levels < 0.2 ng/mL within 12 months of surgery, while sRT was defined when radiation is initiated at PSA level ≥ 0.2 ng/mL or after 12 months of surgery. The prostatic fossa and periprostatic tissues were irradiated to a mean dose of 70.2 Gy using three-dimensional conformal RT, intensity-modulated RT techniques, or proton therapy. GC scores were calculated based on the pre-defined 22-marker Decipher classifier [14]. The GC score is a continuous score between 0 and 1, with the lowest scores indicating a lower risk of metastasis. Patients with GC > 0.6 were categorized as high risk; 0.45–0.6 as average risk; and < 0.45 as low risk [15].

Endpoint

Our endpoint consisted of CR, defined as evidence of disease recurrence in the prostatic fossa, and/or radiographically on computed tomography scan, bone scan, and/or other imaging modalities. Follow-up time was calculated from the time of surgery to time of CR, or time of last available contact, whichever occurred first. Patients who died without CR were censored for the purpose of our analysis.

Statistical analysis

Medians and interquartile ranges (IQRs) were reported for continuous variables, while proportions and frequencies were reported for categorical variables. The Mann–Whitney-U test and chi-square tests were used to compare continuous and categorical variables, respectively.

Kaplan–Meier curves were used to estimate CR rates in the entire cohort and after stratifying patients based on aRT status. The log-rank test was used to compare CR rates between these groups.

Our statistical analysis consisted of several steps. First, we used the time-dependent concordance index (c-index) to examine the accuracy of the original model in our cohort [16]. Second, calibration plots assessed the overall extent of over-or-under-estimation of CR rates compared with the nomogram-predicted probability of CR. Finally, the decision-curve analysis examined the net-benefit of using this model in our cohort using the methodology described by Vickers et al. [17].

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Two-sided statistical significance was defined as a p-value < 0.05.

Results

The median (IQR) follow-up of the cohort was 26.5 (17.48–36.44) months. The median age (IQR) of the cohort was 64 (58–68) years. The median (IQR) PSA of the cohort

was 5.9 (4.6–9) ng/mL. 19.6% of the cohort had Gleason score 8 or higher. Non organ-confined disease (pT3a/b) was noted in 238/350 (67.6%) of the cohort. A positive surgical margin was documented in 337/350 (95.74%) of the patients. Overall, 14% (49/350) of the patients received aRT. Patients who received aRT had a higher GC score (0.8 vs. 0.5), higher Gleason score 8 or above (55.1% vs.13.95%), higher pathological stage (pT3b: 55.1% vs.14.6%), and a higher rate of LNI (10.2% vs. 1.66%) compared with men treated with initial observation (all $P < 0.01$) (Table1).

During the follow-up period, 12/350 (3.4%) of the patients developed CR. Overall 3-year CR-free survival was 95% (95% confidence interval: 0.92–0.98). The 3-year CR-free survival was 0.88 (0.70–0.96) in patients who received aRT compared to 0.97 (0.93–0.99) in those who were treated with initial observation ($p = 0.05$) (Fig. 1) The predictive accuracy of the nomogram for prediction of CR-free survival was high in our set (c-Index 0.84), with favorable calibration characteristics (Fig. 2). Decision-curve analysis showed a positive net benefit for probabilities range between 0.01 and 0.09, with the highest difference at threshold probability around 0.05. At that threshold, the net benefit is 0.06 for the model, and 0 for treating all the patients (Fig. 3).

Discussion

The management algorithm to administer aRT post-RP is mainly geared by the presence of adverse pathological, post-op PSA value, and PSA kinetics [8]. Nevertheless, aRT is associated with increased treatment-related toxicity and decreased quality-adjusted life expectancy. Subsequently, only 30% of high-risk patients with a projected life expectancy of more than ten years received aRT therapy [18]. To better identify patients who might benefit the most from administering aRT therapy, and avoiding overtreatment, Dalela et al. developed a GC based risk-stratification tool, which is the first tool that accounts tumor biology features to direct the decision to administer aRT [10].

Compared to the original cohort, on which the nomogram had been developed, patients in our study cohort were older (64 vs. 61 years), had lower PSA at presentation (5.9 vs. 8.1 ng/mL), and had higher decipher score (0.5 vs. 0.41). These differences emphasize the necessity of this study to reflect the applicability of this nomogram in the current practice.

This current study provides external validation of the GC based risk-stratification tool using a contemporary cohort of men who underwent RP between 2013 and 2018. The predictive accuracy of the nomogram for the prediction of CR-free survival was high in this cohort (c-Index = 0.84), with optimal calibration characteristics. These findings support the validity of the abovementioned nomogram in its ability to provide a clinically meaningful improvement in the predictability of CR in contemporary practice.

Finally, the decision curve analysis showed that the model has a significant net-benefit, and as such, can improve the decision-making process in comparison to scenarios where no patient gets aRT(more similar to the current practice), or where all patients get aRT (more similar to the current

Table 1 Descriptive characteristics of 350 patients with prostate cancer treated with radical prostatectomy at a single, high-volume, tertiary medical center between 2013 and 2018

	Grouping	Total cohort ($N = 350$)	No aRT ($N = 301$)	aRT ($N = 49$)	P-Value
Age, years, median (IQR)		64 (58—68)	64 (58—68)	65 (58—68)	0.26
BMI, Kg/m2, median (IQR)		27.9 (25.1—30.6)	27.6 (25.1—30.2)	30 (26.1—32.5)	0.01
Pre-operative PSA, ng/mL, median (IQR)		5.9 (4.6—9)	5.8 (4.5—8.8)	6.4 (5—10.1)	0.19
Decipher score		0.5 (0.3—0.7)	0.5 (0.3—0.7)	0.8 (0.7—0.9)	< 0.001
Pathological Gleason score, n (%)	6	7 (1.%)	7 (2.33%)	0 (0%)	< 0.001
	7	276 (78.41%)	252 (83.72%)	22 (44.9%)	
	8	43 (12.22%)	26 (8.64%)	17 (34.69%)	
	≥ 9	26 (7.39%)	16 (5.32%)	10 (20.41%)	
Surgical Margin, *n* (%)	Missing	2 (0.57%)	2 (0.66%)	0 (0%)	NA
	Negative	13 (3.69%)	12 (3.99%)	0 (0%)	
	Positive	337 (95.74%)	287 (95.35%)	49 (100%)	
Pathological Staging N, *n* (%)	N0	341 (96.88%)	296 (98.34%)	44 (89.8%)	0.01
	N1	11 (3.13%)	5 (1.66%)	5 (10.2%)	
Pathological Staging T, *n* (%)	≤ T2c	114 (32.39%)	108 (35.88%)	5 (10.2%)	< .001
	T3a	166 (47.16%)	149 (49.5%)	17 (34.69%)	
	T3b	72 (20.45%)	44 (14.62%)	27 (55.1%)	

aRT, Adjuvant radiation therapy; BMI: Body mass index;

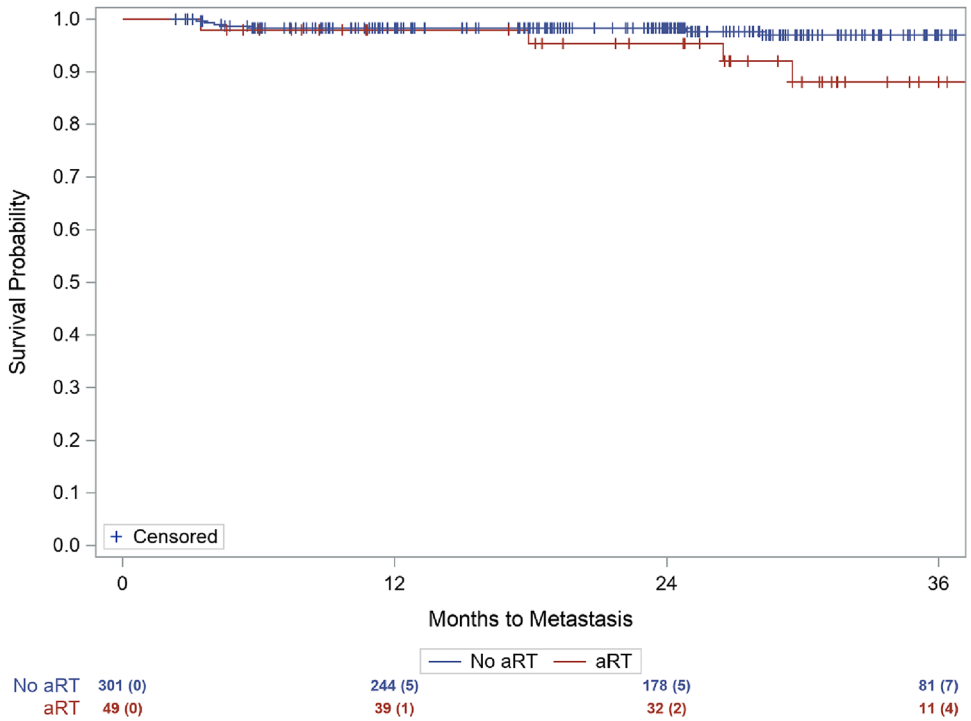

Fig. 1 Kaplan-Meier curve depicts the 3-year CR-free survival in the cohort

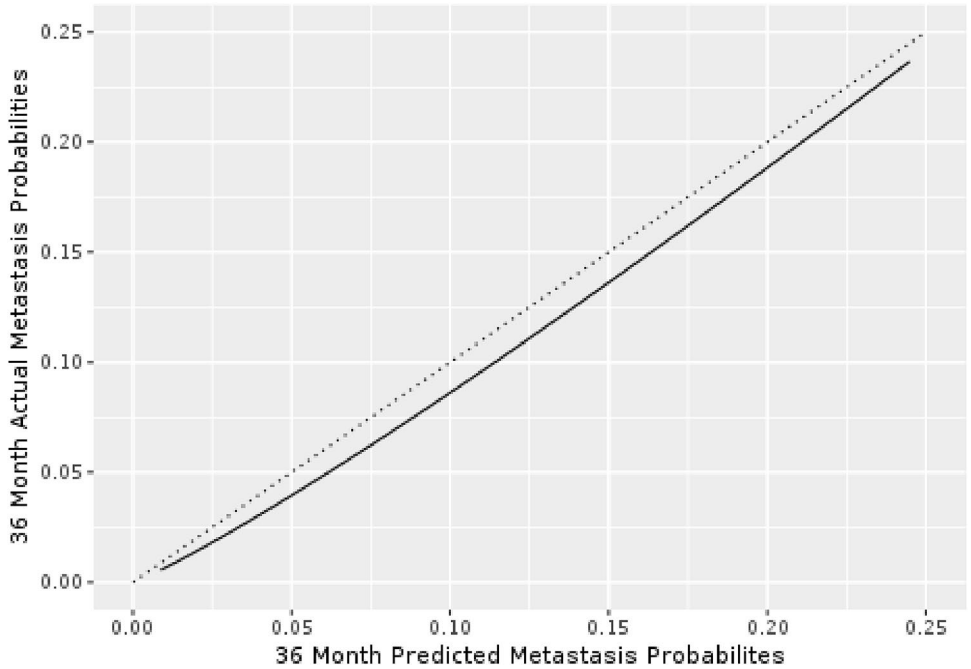

Fig. 2 Calibration characteristics of the nomograms using the contemporary data

recommendations, based on the aRT trial results) [7, 8]. Interestingly, there was no difference in the 3-year CR-free survival in this cohort in patients who received aRT and patients treated with initial observation. This might reflect the current sagacious approach of offering aRT to patients with several adverse pathological features and high GC score. Meanwhile, observing patients with few adverse pathological features and low GC score might be beneficial, along with treating patients with early sRT in the event of biochemical progression as the case in 19.9%(60/301) of the patients in the initial observation group. This observation is in line with the results from the ARTISTIC metanalysis of three randomized trials, RADICALS (ISRCTN40814031), GETUG-AFU 17 (NCT00667069), and RAVES (NCT00860652),; which showed that early sRT is not inferior to aRT [19].

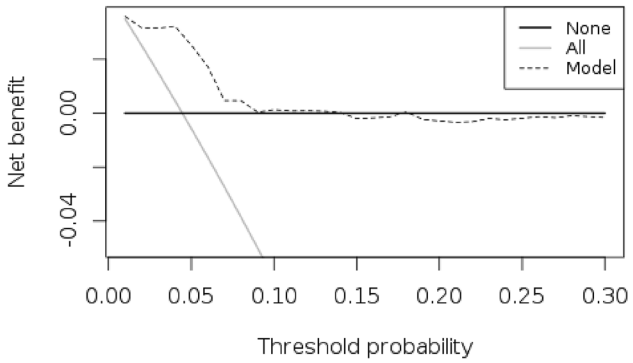

Fig. 3 Decision curves analysis plots measured at 36 months following radical prostectomy for clinical recurrence free survival

That said, it is noteworthy that the percentage of patients with multiple adverse pathology features was very low in these trials (~20%).These individuals are most likely to benefit from aRT rather than sRT, as previously demonstrated by Abdollah et al. and Dalela et al. [10, 20]. The low percentage of these individuals in the ARTISTIC metanalysis limits the applicability of its results. As such, the efficacy of early sRT in patients with multiple adverse pathological features remains to be demonstrated in future studies. Meanwhile, the Dalela et al. nomogram can be a great tool to guide treatment decision in these individuals.

Our study has several limitations that warrant discussion. For example, our patients were treated at a single, high-volume, tertiary medical center; therefore, we cannot exclude inherent selection bias due to referral pattern and insurance coverage. Likewise, there was a wide variation in the post-surgical treatment regime. Specifically, in addition to the variation in the type of adjuvant radiotherapy offered (e.g., external beam radiotherapy, intensity-modulated radiotherapy, and proton-beam radiotherapy), aRT was offered under a range of conditions, including in combination with androgen deprivation therapy, and whole pelvic radiation. Finally, the short follow-up of this cohort represents another limitation and precludes analysis of CR at later time points (e.g., > 5 years).

Conclusions

Our Findings are the first to validate the GC-based stratification model proposed by Dalela et al. and shows its utility in a contemporary setting. Moreover, our results show that patients with multiple adverse pathology features and high CG scores are most likely to benefit aRT rather than salvage RT (sRT).This model can be used to advise patients in everyday clinical work, as well as to stratify patients for the purpose of future randomized clinical trials, examining the impact of post-operative radiotherapy.

Acknowledgments Nothing to Acknowledge

Author contributions DIL: concept, manuscript writing. MS: concept, data collection, manuscript writing. DD: manuscript editing. JK: data analysis. PL: manuscript editing. NV: manuscript editing. FA: result interpretation, manuscript writing and editing.

Funding None.

Availability of data and material Upon reviewer request.

Compliance with ethical standards

Conflict of interest Firas Abdollah is a consultant for GenomeDx Biosciences.

Ethical approval Approved by the IRB of the University of Pennsylvania.

References

1. Hager B, Kraywinkel K, Keck B, Katalinic A, Meyer M, Zeissig SR, Scheufele R, Wirth MP, Huber J (2017) Increasing use of radical prostatectomy for locally advanced prostate cancer in the USA and Germany: a comparative population-based study. Prostate Cancer Prostatic Dis 20(1):61–66
2. - Briganti A, Karnes RJ, Gandaglia G, Spahn M, Gontero P, Tosco L, Kneitz B, Chun FK, Zaffuto E, Sun M, Graefen M. Natural history of surgically treated high-risk prostate cancer. InUrologic Oncology: Seminars and Original Investigations 2015. (Vol. 33, No. 4, pp. 163-e7). Elsevier.
3. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, Partin AW (2005) Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 294(4):433–439
4. Thompson IM Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, Messing E, Forman J, Chin J, Swanson G, Canby-Hagino E, Crawford ED (2006) Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 296(19):2329–2335
5. -Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, Verbaeys A, Bosset JF, van Velthoven R, Colombel M, van de Beek C, Verhagen P, van den Bergh A, Sternberg C, Gasser T, van Tienhoven G, Scalliet P, Haustermans K, Collette L; European Organisation for Research and Treatment of Cancer, Radiation Oncology and Genito-Urinary Groups. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet. 2012 Dec 8;380(9858):2018–27.
6. Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, Willich N, Semjonow A, Souchon R, Stöckle M, Rübe C, Weissbach L, Althaus P, Rebmann U, Kälble T, Feldmann HJ, Wirth M, Hinke A, Hinkelbein W, Miller K (2009) Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96–02/AUO AP 09/95. J Clin Oncol 27(18):2924–2930
7. -Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, Mottet N; European Association of Urology. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol. 2014;65(1):124–37.

8. Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, Hahn C, Klein E, Michalski J, Roach M, Sartor O, Wolf JS Jr, Faraday MM (2013) Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol 190(2):441–449
9. Ross AE, Feng FY, Ghadessi M, Erho N, Crisan A, Buerki C, Sundi D, Mitra AP, Vergara IA, Thompson DJ, Triche TJ (2014) A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. Prostate cancer and prostatic diseases 17(1):64
10. Dalela D, Santiago-Jiménez M, Yousefi K, Karnes RJ, Ross AE, Den RB, Freedland SJ, Schaeffer EM, Dicker AP, Menon M, Briganti A, Davicioni E, Abdollah F (2017) Genomic Classifier Augments the Role of Pathological Features in Identifying Optimal Candidates for Adjuvant Radiation Therapy in Patients With Prostate Cancer: Development and Internal Validation of a Multivariable Prognostic Model. J Clin Oncol 35(18):1982–1990
11. Kattan MW (2011) Factors affecting the accuracy of prediction models limit the comparison of rival prediction models when applied to separate data sets. Eur Urol 59:566–567
12. Fleshner K, Carlsson SV, Roobol MJ (2017) The effect of the USPSTF PSA screening recommendation on prostate cancer incidence patterns in the USA. Nat Rev Urol 14(1):26–37. https://doi.org/10.1038/nrurol.2016.251
13. -Byrd DR, Carducci MA, Compton CC, Fritz AG, Greene FL. AJCC cancer staging manual. Edge SB, editor. New York: Springer; 2010.
14. Klein EA, Haddad Z, Yousefi K, Lam LL, Wang Q, Choeurng V, Palmer-Aronsten B, Buerki C, Davicioni E, Li J, Kattan MW (2016) Decipher genomic classifier measured on prostate biopsy predicts metastasis risk. Urology 1(90):148–152
15. -spratt DE, Yousefi K, Deheshi S, Ross AE, Den RB, Schaeffer EM, Trock BJ,Zhang J, Glass AG, Dicker AP, Abdollah F, Zhao SG, Lam LLC, du Plessis M,Choeurng V, Haddad Z, Buerki C, Davicioni E, Weinmann S, Freedland SJ, Klein EA, Karnes RJ, Feng FY. Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease. J Clin Oncol. 2017;35(18):1991–1998.
16. Gerds TA, Kattan MW, Schumacher M, Yu C (2013) Estimating a time-dependent concordance index for survival prediction models with covariate dependent censoring. Stat Med 32(13):2173–2184
17. Vickers AJ, Elkin EB (2006) Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 26(6):565–574
18. Sineshaw HM, Gray PJ, Efstathiou JA, Jemal A (2015) Declining Use of Radiotherapy for Adverse Features After Radical Prostatectomy: Results From the National Cancer Data Base. Eur Urol 68(5):768–774
19. -C L Vale, M Brihoum, S Chabaud, A Cook, D Fisher, S Forcat, C Fraser-Browne, A Herschtal, A Kneebone, S Nénan, C Parker, M K B Parmar, M Pearse, P Richaud, E Rogozińska, P Sargos, M R Sydes, J F Tierney, LBA48_PR .Adjuvant or salvage radiotherapy for the treatment of localised prostate cancer? A prospectively planned aggregate data meta-analysis, Annals of Oncology. 30 (Supplement_5), 2019, mdz394.041
20. Abdollah F, Suardi N, Cozzarini C, Gallina A, Capitanio U, Bianchi M, Sun M, Fossati N, Passoni NM, Fiorino C, Di Muzio N, Karakiewicz PI, Rigatti P, Montorsi F, Briganti A (2013) Selecting the optimal candidate for adjuvant radiotherapy after radical prostatectomy for prostate cancer: a long-term survival analysis. Eur Urol 63(6):998–1008