



# Genomic classifier for guiding treatment of intermediate-risk prostate cancers to dose-escalated image-guided radiotherapy without hormone therapy

DOI:

[10.1016/j.ijrobp.2018.08.030](https://doi.org/10.1016/j.ijrobp.2018.08.030)

## Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

## Citation for published version (APA):

Berlin, A., Murgic, J., Hosni, A., Pintilie, M., Salcedo, A., Fraser, M., Kamel-Reid, S., Zhang, J., Wang, Q., Ch'ng, C., Deheshi, S., Davicioni, E., van der Kwast, T., Boutros, P. C., Bristow, R. G., & Chua, M. L. K. (2018). Genomic classifier for guiding treatment of intermediate-risk prostate cancers to dose-escalated image-guided radiotherapy without hormone therapy. *International journal of radiation oncology, biology, physics*.  
<https://doi.org/10.1016/j.ijrobp.2018.08.030>

## Published in:

International journal of radiation oncology, biology, physics

## Citing this paper

Please note that where the full-text provided on Manchester Research Explorer is the Author Accepted Manuscript or Proof version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version.

## General rights

Copyright and moral rights for the publications made accessible in the Research Explorer are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

## Takedown policy

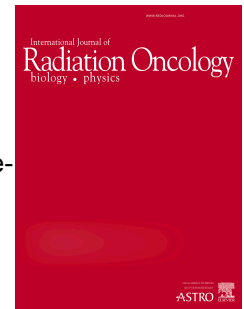
If you believe that this document breaches copyright please refer to the University of Manchester's Takedown Procedures [<http://man.ac.uk/04Y6Bo>] or contact [uml.scholarlycommunications@manchester.ac.uk](mailto:uml.scholarlycommunications@manchester.ac.uk) providing relevant details, so we can investigate your claim.



# Accepted Manuscript

Genomic classifier for guiding treatment of intermediate-risk prostate cancers to dose-escalated image-guided radiotherapy without hormone therapy

Alejandro Berlin, Jure Murgic, Ali Hosni, Melania Pintilie, Adriana Salcedo, Michael Fraser, Suzanne Kamel-Reid, Jingbin Zhang, Qiqi Wang, Carolyn Ch'ng, Samineh Deheshi, Elai Davicioni, Theodorus van der Kwast, Paul C. Boutros, Robert G. Bristow, Melvin L.K. Chua



PII: S0360-3016(18)33636-8

DOI: [10.1016/j.ijrobp.2018.08.030](https://doi.org/10.1016/j.ijrobp.2018.08.030)

Reference: ROB 25255

To appear in: *International Journal of Radiation Oncology • Biology • Physics*

Received Date: 24 June 2018

Revised Date: 8 August 2018

Accepted Date: 19 August 2018

Please cite this article as: Berlin A, Murgic J, Hosni A, Pintilie M, Salcedo A, Fraser M, Kamel-Reid S, Zhang J, Wang Q, Ch'ng C, Deheshi S, Davicioni E, van der Kwast T, Boutros PC, Bristow RG, Chua MLK, Genomic classifier for guiding treatment of intermediate-risk prostate cancers to dose-escalated image-guided radiotherapy without hormone therapy, *International Journal of Radiation Oncology • Biology • Physics* (2018), doi: 10.1016/j.ijrobp.2018.08.030.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

# Genomic classifier for guiding treatment of intermediate-risk prostate cancers to dose-escalated image-guided radiotherapy without hormone therapy

Alejandro Berlin<sup>1,2,3</sup>, Jure Murgic<sup>1</sup>, Ali Hosni<sup>1</sup>, Melania Pintilie<sup>1</sup>, Adriana Salcedo<sup>4,5</sup>, Michael Fraser<sup>4</sup>, Suzanne Kamel-Reid<sup>6</sup>, Jingbin Zhang<sup>7</sup>, Qiqi Wang<sup>7</sup>, Carolyn Ch'ng<sup>7</sup>, Samineh Deheshi<sup>7</sup>, Elai Davicioni<sup>7</sup>, Theodorus van der Kwast<sup>6</sup>, Paul C. Boutros<sup>4,5,8</sup>, Robert G. Bristow<sup>1,2,9,\*</sup>, Melvin L.K. Chua<sup>1,10,11,\*</sup>.

<sup>1</sup>Princess Margaret Cancer Centre, University Health Network, Ontario, Canada;

<sup>2</sup>Department of Radiation Oncology, University of Toronto, Ontario, Canada;

<sup>3</sup>Techna Institute, University Health Network, Ontario, Canada;

<sup>4</sup>Informatics and Biocomputing Program, Ontario Institute for Cancer Research, Ontario, Canada;

<sup>5</sup>Department of Medical Biophysics, University of Toronto, Ontario, Canada;

<sup>6</sup>Laboratory Medicine Program, University Health Network, Ontario, Canada;

<sup>7</sup>GenomeDx Biosciences Inc. Vancouver, British Columbia, Canada;

<sup>8</sup>Department of Pharmacology and Toxicology, University of Toronto, Ontario, Canada;

<sup>9</sup>Manchester Cancer Research Centre, Manchester, UK;

<sup>10</sup>Divisions of Radiation Oncology and Medical Sciences, National Cancer Centre Singapore, Singapore;

<sup>11</sup>Oncology Academic Program, Duke-NUS Medical School, Singapore.

- These authors contributed equally

**Key words:** prostate cancer; intermediate-risk; radiotherapy; genomics; prognostication.

## Funding support:

This study was conducted with the support of The Terry Fox Research Institute (TFRI) to the Canadian Prostate Cancer Biomarker Network (CPCBN), and Movember funds

through Prostate Cancer Canada (PCC). AB is supported by the Ontario Association of Radiation Oncologist Clinician Scientist Award. PCB was supported by a TFRI New Investigator Award, a PCC Rising Star Fellowship, and a CIHR New Investigator Award. The authors gratefully thank the Princess Margaret Cancer Centre Foundation and Radiation Medicine Program Academic Enrichment Fund for support. RGB is a recipient of a Canadian Cancer Society Research Scientist Award. MC is supported by the National Medical Research Council Singapore Transition Award and Duke-NUS Oncology Academic Program Proton Research Fund.

**#Corresponding authors:**

Melvin L.K. Chua

Division of Radiation Oncology,

National Cancer Centre Singapore.

11 Hospital Drive, Singapore 169610.

Tel: (65) 6321 4710; Fax: (65) 6222 8675

Email: [Melvin.chua.l.k@singhealth.com.sg](mailto:Melvin.chua.l.k@singhealth.com.sg)

Robert G Bristow

Manchester Cancer Research Centre

555 Wilmslow Road, Manchester M20 4GJ

Tel: +44(0)161 306 3249

Email: [robert.bristow@manchester.ac.uk](mailto:robert.bristow@manchester.ac.uk)

**Disclosure of potential conflicts of interest**

JZ, QW, CC, SD and ED are employees of Genome DX. ED holds shares of Genome DX, and has a patent filled related to the present work. Other authors declare no conflict of interest.

**Word counts:** 2334 (main text), 265 (abstract)

**Total number of figures:** 2 (2 Supplementary Figures)

**Total number of tables:** 3 (2 Supplementary Tables)

# Genomic classifier for guiding treatment of intermediate-risk prostate cancers to dose-escalated image-guided radiotherapy without hormone therapy

XXXXXX

- These authors contributed equally

**Key words:** prostate cancer; intermediate-risk; radiotherapy; genomics; prognostication.

**Funding support:**

XXXXXX

**#Corresponding authors:**

XXXXX

**Disclosure of potential conflicts of interest**

XXXXXXX

## Abstract

**Background:** The NCCN has recently endorsed the stratification of intermediate-risk prostate cancer (IR-PCa) into favorable and unfavourable subgroups, and recommend the addition of androgen deprivation therapy (ADT) to radiotherapy (RT) for unfavorable IR-PCa. Recently, more accurate prognostication was demonstrated by integrating a 22-feature genomic classifier (GC) to the NCCN stratification system. Here, we test the utility of the GC to better identify IR-PCa patients who are sufficiently treated by RT alone.

**Methods:** We identified a novel cohort comprising 121 IR-PCa patients treated with dose-escalated image-guided RT (DE-IGRT; 78 Gy in 39 fractions) without ADT. GC scores were derived from tumor sampled in diagnostic biopsies. Multivariable analyses including both NCCN subclassification and GC scores were performed for biochemical failure (PSA nadir + 2 ng/ml) and metastasis occurrence.

**Results:** By NCCN subclassification, 33 (27.2%) and 87 (71.9%) of men were classified as favorable and unfavorable IR-PCa, respectively (1 case unclassifiable). GC scores were high in 3 favorable IR-PCa, and low in 60 unfavorable IR-PCa. Higher GC scores, but not NCCN-risk subgroups, were associated with biochemical relapse (HR 1.36 [95%CI=1.09-1.71] per 10% increase,  $P=0.007$ ) and metastasis (HR 2.05 [95%CI=1.24-4.24],  $P=0.004$ ). GC predicted biochemical failure at 5-year (AUC 0.78 [95%CI 0.70-0.83]), and the combinatorial NCCN+GC model significantly outperformed the NCCN alone model for predicting early-onset metastasis (AUC 5-year metastasis = 0.89 vs 0.86 [GC alone] vs 0.54 [NCCN alone]).

**Conclusions:** We demonstrated the accuracy of the GC for predicting disease recurrence in IR-PCa treated with DE-IGRT alone. Our findings highlight the need to evaluate this GC in a prospective clinical trial investigating the role of ADT-RT in clinicogenomic-defined IR-PCa subgroups.

**Summary:** We demonstrate the utility of GC over the existing NCCN subclassification for predicting disease outcomes (biochemical recurrence and metastasis) in IR-PCa. We therefore recommend the use of clinicogenomic risk stratification to identify IR-PCa patients who can be treated with DE-IGRT and safely omit combinatorial ADT.

## Introduction

Image-guided radiation therapy (IGRT) represents a primary treatment modality for localized prostate cancer (1). Prospective evidence supports combination androgen deprivation therapy (ADT) with IGRT to both improve local control (i.e. radiosensitization) and target occult metastases (2), reducing the disease-specific mortality in high-risk prostate cancer (3, 4). However, the benefit of systemic intensification is debatable for intermediate-risk prostate cancer (IR-PCa), especially when treated with dose-escalated IGRT (DE-IGRT). The NCCN now endorses factoring in additional factors to subclassify an unfavorable IR-PCa subgroup, who are at higher risk of metastatic relapse and prostate cancer-specific mortality (5), and therefore more likely to benefit from combined modality treatments such as ADT with RT (4, 6, 7).

Comprehensive molecular profiling of IR-PCa has revealed multiple genomic features of aggression within tumor foci harboring the same histomorphological grade (8, 9), highlighting the role of genomics for enhanced prognostication beyond conventional indices. On this note, a clinically approved RNA-based 22-gene genomic classifier (GC, [Decipher, GenomeDx BioSciences]) has been validated as a stratification tool for risk of metastatic relapse, PCa-specific mortality, and predicting response to postoperative RT (10-13). Additionally, the 22-gene GC has been included in a novel clinicogenomic classification that was proposed to represent a more precise method for risk-stratifying localized PCa (14).

Here, we evaluate the validity of the 22-gene GC test performed on diagnostic biopsies, accounting for clinicopathologic NCCN risk grouping, for predicting



biochemical and metastatic relapse in a cohort of IR-PCa treated with single-modality DE-IGRT at a tertiary cancer center. Of note, there has been only one other prior study reporting on the utility of a biopsy-derived GC score, and it focused on a mixed cohort of intermediate- and high-risk PCa treated with combined ADT and RT (15). We show that the GC score outperforms the NCCN criteria in distinguishing IR-PCa patients with favorable outcomes after DE-IGRT without ADT from those who are at risk of metastatic relapse. The GC test may thus be useful for personalizing treatment strategies in IR-PCa, providing actionable information to identify men who ought to receive combination ADT to DE-IGRT.

## Materials and methods

### *Study Cohort*

After obtaining institutional approval (XXXXX), we queried our prospective registry between 2005 and 2011 to identify men diagnosed with NCCN-defined IR-PCa treated with curative-intent DE-IGRT without neoadjuvant, concomitant or adjuvant ADT. All patients underwent dedicated computed tomography (CT) simulation. The PTV was created by adding 1 cm isotropic expansion in all directions except 7 mm posteriorly to the prostate and caudal 1-2cm of seminal vesicles. All patients received 78 Gy (2.0 Gy per fraction) delivered by intensity-modulated radiotherapy (IMRT), with daily image-guidance based on fiducial- and/or soft tissue-based matching on cone-beam CT.

During the study period, diagnostic systematic biopsies consist of 11-12 samples obtained under transrectal ultrasound guidance. Pathology database was cross-referenced to identify those who had prostate core biopsies paraffin-embedded blocks available in-house for genomic characterization. Clinical and genomic data were collected and added to the GenomeDx prostate cancer genomic resource information database (GRID<sup>TM</sup>, NCT02609269). This is therefore an unpublished cohort with complete clinical and genomic annotation.

### *Specimen Collection and Processing*

Hematoxylin and eosin stained slides of diagnostic prostate biopsies were centrally reviewed by an expert GU pathologist (XXXX) for demarcating representative cores containing the highest GS, and  $\geq 6$  mm tumor length with  $\geq 70\%$  cellularity. Two distinct

tumor regions were demarcated and punched (2 mm-diameter) from the corresponding paraffin blocks. Total RNA was extracted in a CLIA-certified laboratory using Maxwell 16 LEV RNA FFPE Kit (Promega, Madison, Wisconsin) as per specifications. RNA was labeled and hybridized to Human Exon 1.0 ST microarrays (Affymetrix, Santa Clara, California) by GenomeDx Biosciences Laboratory (San Diego, California) using the Decipher CLIA-certified commercial platform, as previously described (10). Microarray quality control was performed using the Affymetrix Power Tools packages (16). Probeset summarization and normalization was subsequently performed using the single channel array normalisation (SCAN) algorithm (17).

#### *Calculation of GC score and NCCN subclassification*

The 22-gene GC score was determined from the Decipher prostate cancer classifier assay (GenomeDx Biosciences Laboratory, San Diego, California) as previously described (10, 15, 18). Briefly, GC was calculated based on a locked random forest model to produce a score between 0 and 1. Formerly established cut-points of 0.45 and 0.6 for GC were used for categorical analyses. As per NCCN-endorsed subclassification, unfavorable IR-PCa was defined as any patient with a primary Gleason grade 4 and/or percentage of positive biopsy cores  $\geq 50\%$  and/or  $\geq 2$  NCCN intermediate-risk factors (5).

#### *Statistical considerations*

The primary and secondary endpoints of the study were biochemical failure and metastasis occurrence, respectively. Biochemical failure was defined as per Phoenix criteria (PSA nadir + 2ng/mL). The performance of the GC to predict response to DE-IGRT was evaluated by its ability to: 1) independently predict biochemical failure and metastasis following DE-IGRT using multivariable (MVA) Cox regression with Firth's penalized bias reduction method; 2) stratify biochemical failure and metastasis rate among patients using Kaplan-Meier survival curves with an adaptation of Fine-Gray analysis; and 3) discriminate biochemical failure and metastasis rate among patients using survival receiver operating characteristic curves (ROC) at 5 years (19). The survival C-index of the combined models was estimated by subjecting the model to bootstrapping with 500 resamples for optimism correction. Ninety-five percent confidence intervals (95%CI) for the C-index were computed using bootstrapping methods. Decision curve analysis was performed to evaluate the net benefit of GC and NCCN across clinically relevant threshold probabilities. Statistical significance was defined by  $P < 0.05$ . All analyses were performed in R v3.3 (R Foundation for Statistical Computing, Austria).

## Results

A total of 121 patients met our study eligibility criteria, comprising 33 (27.3%) NCCN-favorable and 87 (71.9%) NCCN-unfavorable IR-PCa (**Table 1**). Median follow-up of the cohort was 7.5 years (IQR 6.5-8.7 years). Overall, GC classified 87 (71.9%) patients as low-risk, while 18 (14.9%) and 15 (12.4%) patients were classified as intermediate- and high-risk, respectively. In the NCCN-unfavorable subgroup, GC classified 60 (69.0%), 15 (17.2%) and 12 (13.8%) cases into low-, intermediate-, and high-risk, respectively, while GC stratified 3 of 33 (9.1%) NCCN-favorable IR-PCa patients as high-risk (**Supplementary Figure 1**). Interestingly, the combinatorial NCCN subclassification and GC as per the new clinicogenomic risk grouping system (14) yielded a comparable stratification of high-risk cases to using the GC alone (N = 12 (9.9%), **Table 1**).

We recorded 24 biochemical failures and 5 metastasis occurrences in our cohort. The NCCN IR-PCa subclassification was not associated with risk of biochemical or metastatic relapse ( $P = 0.235$  and  $P = 0.885$  respectively; **Figure 1A**). Conversely, GC scores were a strong predictor of biochemical and metastatic relapses (HR biochemical failure = 1.33 [1.08-1.66],  $P = 0.009$ ; HR metastasis = 2.05 [1.24-4.23],  $P = 0.003$ ; **Figure 1B, Tables 2 and 3, Supplementary Tables 1-2**), even after adjustment for NCCN indices and subclassification, primary Gleason grade 4, and percentage of positive biopsy cores. This corresponded to a substantial improvement in accuracy for prediction of biochemical relapse: AUC = 0.56 (NCCN only) vs 0.78 (GC only) vs 0.85 (NCCN + GC). Similarly, we observed improved prediction for early onset (5-year) metastatic recurrences: AUC = 0.54 (NCCN only) vs 0.86 (GC only) vs 0.89 (NCCN + GC) (**Figure 2**). Therefore, our results expand on the existing literature, and highlight

the utility of the GC score as a clinical decision making tool in addition to the NCCN criteria for selecting IR-PCa to combination ADT-IGRT (**Supplementary Figure 2**).

## Discussion

Here, we aimed to determine the clinical utility of a 22-gene GC in IR-PCa patients treated with radical RT monotherapy, and build on the evidence highlighting the need to improve upon the current prognostication methods for localized prostate cancer. The present study is novel, as it reports on the performance of the GC for predicting adverse outcomes (biochemical failures and lethal metastases) in an unpublished IR-PCa cohort from a high-volume academic center that was treated with single modality DE-IGRT (78 Gy in 39 fractions). Of note, we observed that a substantial proportion of patients (60 of 87) were reclassified as GC low-risk despite harboring unfavorable clinicopathological risk factors. Importantly, the GC outperformed all other indices, including the NCCN subclassification, in predicting biochemical failure and metastasis occurrence after DE-IGRT, with an optimistic accuracy that exceeds 80%. This corresponded to our secondary observation of comparable re-stratification rates to high-risk by GC test alone (12.4%) and the recent clinicogenomic classification system proposed by Spratt and colleagues (9.9%). Hence, our results underscore the clinical impact of incorporating genomic characterization into localized prostate cancer prognostic systems, allowing the identification of a substantial subgroup of IR-PCa patients who can be optimally treated by DE-RT without ADT.

On this note, it is known that IR-PCa represents a clinically heterogeneous subgroup, for which conventional clinicopathological parameters of T-category, PSA, and GS are imprecise for risk stratification, thus commonly leading to under- and over-treatment. Hence, the NCCN recently updated their classification of IR-PCa by including additional diagnostic parameters to further stratify IR-PCa into favorable and

unfavorable subgroups with disparate risks of metastasis and PCa-specific mortality (5). Nonetheless, this subclassification scheme was developed in a heterogeneous cohort of men treated with DE-EBRT, most of whom received androgen deprivation therapy (ADT). This may be consistent with clinical observations that men harboring unfavorable IR-PCa are likely benefited by treatment intensification with addition of ADT to RT (6, 7, 20, 21), but the majority of patients included in these studies were not treated with contemporary escalated doses of RT. It therefore remains undefined if the majority of unfavorable IR-PCa requires combined ADT for radiosensitization (2, 22) and/or targeting occult metastases in the context of increased RT dose intensity. It is expected that the ongoing RTOG 0815 randomized controlled trial (Clinicaltrials.gov; NCT00936390) will determine the incremental benefit of ADT in the context of DE-IGRT, thus providing valuable information for this clinical conundrum in IR-PCa. All this evidence, highlights the pressing need for more accurate, patient-specific, biology-based biomarkers to guide treatment individualization (de)intensification strategies.

Recently, a novel clinicogenomic model was proposed stressing the necessity to incorporate molecular biomarkers (GC) to clinical indices (NCCN classification) for accurate prediction of aggressive PCa (14). Our results support the need for such a model; we observed that combinational NCCN+GC indices yield the strongest discrimination for favorable and unfavorable subtypes of IR-PCa (AUC for 5-year biochemical failure = 0.85 vs 0.78 [GC alone] vs 0.56 [NCCN alone]). Additionally, we propose the potential clinical utility of GC for personalizing treatment recommendations in men with IR-PCa. Men with GC low-risk could be treated with DE-IGRT alone with



expected excellent outcomes, while individuals harboring NCCN unfavorable disease coupled with GC high-risk ought to be considered for combination ADT-RT.

A pertinent design of our study relates to the molecular profiling of tumors that were isolated from diagnostic biopsies, which is crucial when considering the utility of a biomarker to inform on treatment recommendations *a priori*. Notably, the impact of the spatial heterogeneity (8) on the prognostic accuracy of genomic biomarkers remains largely unquantified. Nevertheless, this work adds to other studies that have reported on biopsy-based genomic signatures that predict for aggressive localised PCa, albeit most of these studies utilized mixed cohorts of intermediate- and high-risk PCa who were predominantly treated with ADT-RT (15, 23, 24). Our study is therefore informative, as beyond prognostication it provides potentially actionable information by focusing solely on IR-PCa, for whom current guidelines reflect the clinical challenge of DE-RT alone versus systemic (ADT) and/or local (brachytherapy boost) intensification.

Our study is not devoid of limitations. First, it is arguable that our study is underpowered given the modest sample size and consequently few metastatic events. Nonetheless, our patient cohort was identified from a prospective registry with stringent inclusion criteria of adequate diagnostic biopsy tissue for central pathology review and sampling, omission of concurrent ADT with RT, and contemporary RT dose intensity and technique of 78 Gy in 39 fractions delivered using IGRT. This reflects real-life clinical practice, and the fact that the GC is robust for prognosticating these patients is compelling for its routine clinical implementation in men with IR-PCa treated with RT. Next, while we acknowledge that the addition of ADT to RT for unfavorable IR-PCa disease is considered standard practice by several institutions, it remains debatable if

the reported benefits of the combinatorial approach are maintained in the context of RT dose-escalation. Presently, the EORTC 22991 phase III trial provides the main supportive evidence specific to this clinical conundrum (4). However, it must be cautioned that the trial's cohort also consisted of 25% NCCN-defined high-risk patients, treatment schedules with minor dose-escalation (i.e. 70Gy or 74Gy in more than 75% of cases), and delivered without image-guidance; all elements which could in part explain the poor outcomes in the EBRT-alone control arm. Therefore, at the time of the present study our practice for clinical management of IR-PCa remained largely unchanged, and the low rates of biochemical relapse and metastatic events observed support this approach. For example, the 5-year biochemical relapse-free rates in this series were 94% and 88%, respectively, for the favorable and unfavorable subgroups, mirroring the 87% reported in the DE-RT arm from the RTOG 0126 trial in predominantly favorable IR-PCa (25). Nevertheless, we cannot completely exclude the presence of selection bias within this cohort, as in fact during the last years our practice has increasingly embraced combination of DE-IGRT and short-term ADT, particularly in those IR-PCa harbouring unfavourable indices and/or other aggressive features such as intraductal and cribriform subpathologies (26). Finally, although we have shown the potential utility of the GC test for identifying an unfavorable subgroup of men who likely require treatment intensification beyond DE-IGRT, this study is not posed to determine the efficacy of combined ADT-DE-IGRT to overcome the adverse prognosis of patients with a GC high-risk score.

## Conclusions

We report on the robust prediction of biochemical failure and metastasis occurrence using a clinically available GC test in IR-PCa patients who were treated with single modality DE-IGRT. Our study supports the need to evaluate GC in a prospective fashion, as we envisage that the clinicogenomic model could be utilized to personalize treatment intensification with combinatorial ADT and DE-IGRT for IR-PCa patients.

## References

1. Hamdy FC, Donovan JL, Lane JA, *et al.* 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N. Engl. J. Med.* 2016;375:1415–1424.
2. Locke JA, Pra AD, Supiot S, *et al.* Synergistic action of image-guided radiotherapy and androgen deprivation therapy. *Nat Rev Urol.* 2015:1–12.
3. Warde P, Mason M, Ding K, *et al.* Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet.* 2011;378:2104–2111.
4. Bolla M, Maingon P, Carrie C, *et al.* Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991. *J. Clin. Oncol.* 2016;34:1748–1756.
5. Zumsteg ZS, Spratt DE, Pei I, *et al.* A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *European Urology.* 2013;64:895–902.
6. Jones CU, Hunt D, McGowan DG, *et al.* Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N. Engl. J. Med.* 2011;365:107–118.
7. Valicenti RK, Bae K, Michalski J, *et al.* Does hormone therapy reduce disease recurrence in prostate cancer patients receiving dose-escalated radiation therapy? An analysis of Radiation Therapy Oncology Group 94-06. *Int. J. Radiat. Oncol. Biol. Phys.* 2011;79:1323–1329.
8. Boutros PC, Fraser M, Harding NJ, *et al.* Spatial genomic heterogeneity within localized, multifocal prostate cancer. *Nat. Genet.* 2015;47:736–745.
9. Espiritu SMG, Liu LY, Rubanova Y, *et al.* The Evolutionary Landscape of Localized Prostate Cancers Drives Clinical Aggression. *Cell.* 2018;173:1003–1013.e15.
10. Klein EA, Haddad Z, Yousefi K, *et al.* Decipher Genomic Classifier Measured on Prostate Biopsy Predicts Metastasis Risk. *Urology.* 2016;90:148–152.
11. Zhao SG, Chang SL, Spratt DE, *et al.* Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis. *The Lancet Oncology.* 2016;17:1612–1620.
12. Dalela D, Santiago-Jiménez M, Yousefi K, *et al.* 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.* 2017;35:1982–1990.
13. Spratt DE, Yousefi K, Deheshi S, *et al.* 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;35:1991–1998.
14. Spratt DE, Zhang J, Santiago-Jiménez M, *et al.* Development and Validation of a Novel

Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer. *J. Clin. Oncol.* 2018;36:581–590.

15. Nguyen PL, Martin NE, Choeurng V, *et al.* Utilization of biopsy-based genomic classifier to predict distant metastasis after definitive radiation and short-course ADT for intermediate and high-risk prostate cancer. *Prostate Cancer and Prostatic Diseases.* 2017;20:186–192.

16. Lockstone HE. Exon array data analysis using Affymetrix power tools and R statistical software. *Brief. Bioinformatics.* 2011;12:634–644.

17. Piccolo SR, Sun Y, Campbell JD, *et al.* A single-sample microarray normalization method to facilitate personalized-medicine workflows. *Genomics.* 2012;100:337–344.

18. Karnes RJ, Bergstralh EJ, Davicioni E, *et al.* Validation of a Genomic Classifier that Predicts Metastasis Following Radical Prostatectomy in an At Risk Patient Population. *J. Urol.* 2013.

19. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics.* 2000;56:337–344.

20. D'Amico AV, Chen MH, Renshaw AA, *et al.* Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA.* 2008;299:289–295.

21. Keane FK, Chen MH, Zhang D, *et al.* Androgen deprivation therapy and the risk of death from prostate cancer among men with favorable or unfavorable intermediate-risk disease. *Cancer.* 2015;121:2713–2719.

22. Mahamud O, So J, Chua MLK, *et al.* Targeting DNA repair for precision radiotherapy: Balancing the therapeutic ratio. *Current Problems in Cancer.* 2017;41:265–272.

23. Freedland SJ, Gerber L, Reid J, *et al.* Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2013;86:848–853.

24. Jain S, Lyons CA, Walker SM, *et al.* Validation of a Metastatic Assay using biopsies to improve risk stratification in patients with prostate cancer treated with radical radiation therapy. *Annals of Oncology.* 2018;29:215–222.

25. Michalski JM, Moughan J, Purdy J, *et al.* Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk Prostate Cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. *JAMA Oncol.* 2018;4:e180039–e180039.

26. XXXXX.

## Legends

### Tables

**Table 1.** Clinical characteristics of 121 intermediate-risk prostate cancer patients treated with dose-escalated image-guided radiotherapy alone.

**Table 2.** Association of conventional clinical indices, NCCN subclassification, and genomic classifier with biochemical failure.

**Table 3.** Association of conventional clinical indices, NCCN subclassification, and genomic classifier with metastatic relapses.

### Figures

**Figure 1.** (A) Kaplan-Meier plots stratified by NCCN IR-PCa subclassification for biochemical failure (left) and metastatic relapse (right). (B) Univariable analyses for biochemical (left) and metastatic (right) relapses for the different GC-risk categories.

**Figure 2.** Area under the receiver operating characteristic curve (AUC) for prediction of 5-year biochemical (left) and metastatic (right) relapses by the different clinical (NCCN) and genomic (GC and NCCN+GC) models.

### Supplementary Tables

**Table S1.** Univariable and multivariable analyses of biochemical failure risk for categorical genomic classifier (GC) score; low =  $<0.45$ , intermediate =  $0.45-0.60$ , high =  $>0.60$ .

**Table S2.** Univariable and multivariable analyses of metastasis occurrence risk for categorical genomic classifier (GC) score; low =  $<0.45$ , intermediate =  $0.45-0.60$ , high =  $>0.60$ .

### Supplementary Figures

**Figure S1.** Reclassification of NCCN-defined favorable and unfavorable intermediate-risk disease based on GC-defined risk.

**Figure S2.** Decision curve analysis for NCCN criteria and GC for 5-year biochemical failure after dose-escalated image-guided radiotherapy.

## Tables

**Table 1.** Clinical characteristics of intermediate-risk prostate cancer patients treated with dose-escalated image-guided radiotherapy alone.

Clinical parameters	N = 121 (%*)
Median follow-up, years (range)	7.7 (0.7-11.2)
Age, years (median, IQR)	72.4 (68.4-75.0)
Pre-diagnostic PSA, ng/ml (median, IQR)	7.8 (5.7-11.2)
Clinical T-category	
cT1c/T2a	95 (78.5)
cT2b/T2c	26 (21.5)
ISUP grade (GS)	
1 (3+3)	12 (9.9)
2 (3+4)	75 (62.0)
3 (4+3)	34 (28.1)
Percentage of positive biopsy cores	
<50%	69 (57.0)
≥50%	48 (39.7)
Unknown	4 (3.3)
NCCN subclassification	
Favorable	33 (27.3)
Unfavorable <sup>#</sup>	87 (71.9)
Unknown	1 (0.8)
Genomic Classifier score	
Low (<0.45)	88 (72.7)
Intermediate (0.45-0.6)	18 (14.9)
High (>0.6)	15 (12.4)
Clinical-Genomic Risk Group	
Low (0-1)	27 (22.3)
Intermediate (2-3)	81 (66.9)
High (4-5)	12 (9.9)
Unknown	1 (0.8)
Treatment	
IGRT 78 Gy in 39 fractions	121 (100)
Combinatorial ADT	0 (0)

\*Percentages unless otherwise indicated. <sup>#</sup>Patients were classified as unfavorable if they harbor any of three adverse features – 1) percentage of positive biopsy cores ≥50%; 2) primary Gleason's grade 4; 3) two or three NCCN intermediate-risk factors (cT2b-c, GS 7, and PSA >10 ng/ml). Abbreviations: GS = Gleason's score; ISUP = international society of urological pathology grading system for prostate cancer based on GS; IGRT = image-guided radiotherapy; ADT = androgen deprivation therapy; IQR = interquartile range.

**Table 2.** Association of conventional clinical indices, NCCN subclassification, and genomic classifier (GC) with biochemical failure.

Models	Covariates	Univariable		Multivariable (24 events)	
		HR (95% CI)	P-value	HR (95% CI)	P-value
I	<b>Age (continuous)</b>	1.01 (0.93-1.09)	0.895	1.00 (0.91-1.10)	0.928
	<b>Pre-diagnostic PSA (continuous)</b>	1.37 (0.77-2.47)	0.287	1.20 (0.62-2.32)	0.587
	<b>cT-category</b> T2b/c vs T1/T2a (ref)	1.26 (0.50-3.17)	0.627	0.70 (0.22-2.21)	0.544
	<b>ISUP grade</b> 3 vs 2 & 1 (ref)	1.96 (0.87-4.43)	0.105	2.31 (0.96-5.60)	0.063
	<b>Percentage of positive biopsy cores</b> ≥50 vs <50 (ref)	1.54 (0.65-3.63)	0.326	1.50 (0.59-3.78)	0.395
	<b>GC score (continuous)*</b>	<b>1.33 (1.08-1.66)</b>	<b>0.009</b>	<b>1.36 (1.08-1.71)</b>	<b>0.010</b>
II	<b>NCCN subclassification</b> Unfavorable vs Favorable (ref)	1.92 (0.65-5.65)	0.235	1.63 (0.55-4.82)	0.381
	<b>GC score (continuous)*</b>			<b>1.36 (1.09-1.71)</b>	<b>0.007</b>
III	<b>ISUP grade</b> 3 vs 2 & 1 (ref)			2.0 (0.88-4.50)	0.096
	<b>GC score (continuous)*</b>			<b>1.33 (1.08-1.64)</b>	<b>0.008</b>

Abbreviations: ref = reference; ISUP = international society of urological pathology grading system for prostate cancer based on Gleason's score, GC = genomic classifier.



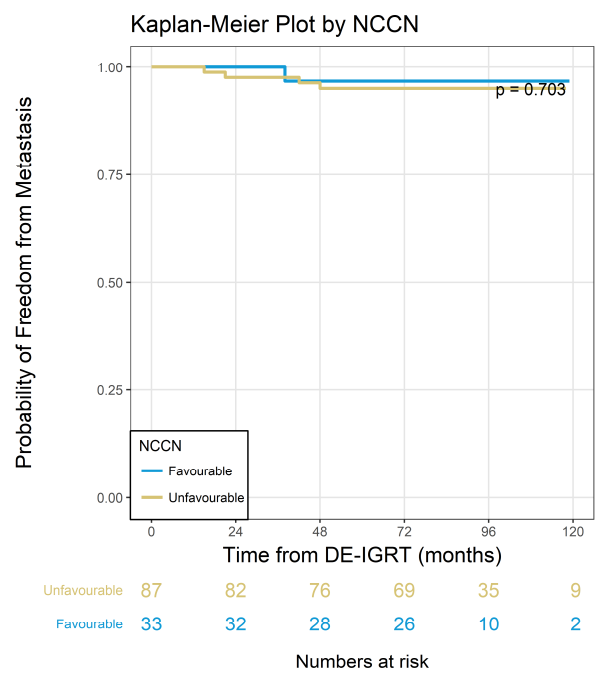
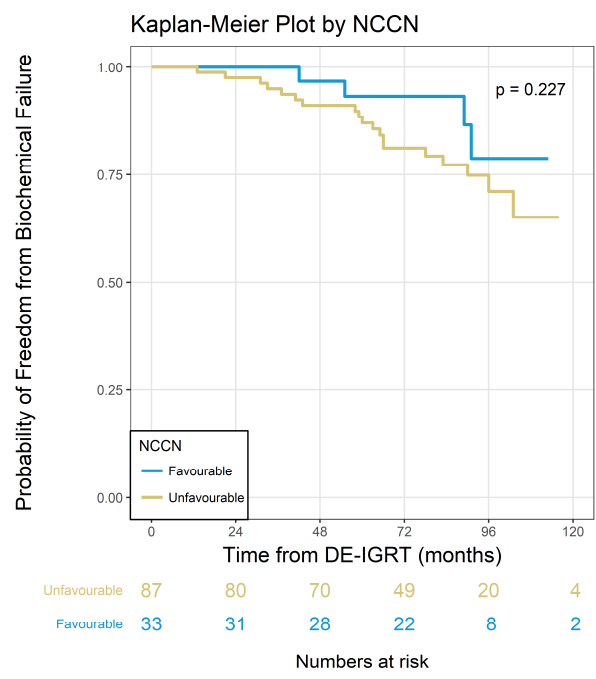
**Table 3.** Association of conventional clinical indices, NCCN subclassification, and genomic classifier (GC) with metastatic relapses.

Models	Covariates	Univariable		Multivariable (5 events)	
		HR (95% CI)	P-value	HR (95% CI)	P-value
I	Age (continuous)	0.98 (0.84-1.17)	0.790	1.14 (0.95-1.40)	0.156
	Pre-diagnostic PSA (continuous)	1.09 (0.36-4.21)	0.892	1.11 (0.17-9.28)	0.912
	cT-category T2b/c vs T1/T2a (ref)	1.30 (0.13-7.02)	0.785	0.25 (0.00-3.04)	0.316
	ISUP grade 3 vs 2 & 1 (ref)	<b>8.12 (1.50-81.0)</b>	<b>0.014</b>	<b>7.92 (1.30-84.50)</b>	<b>0.025</b>
	Percentage of positive biopsy cores ≥50 vs <50 (ref)	1.53 (0.24-9.92)	0.634	0.83 (0.06-9.39)	0.876
	GC score (continuous)*	<b>2.05 (1.24-4.23)</b>	<b>0.003</b>	<b>2.07 (1.17-5.24)</b>	<b>0.010</b>
II	NCCN sub-classification Unfavorable vs Favorable (ref)	1.14 (0.21-11.41)	0.885	0.74 (0.13-7.50)	0.760
	GC score (continuous)*			<b>2.05 (1.24-4.24)</b>	<b>0.004</b>
III	ISUP grade 3 vs 2 & 1 (ref)			<b>6.95 (1.25-70.13)</b>	<b>0.026</b>
	GC score (continuous)*			<b>1.84 (1.18-3.57)</b>	<b>0.006</b>

Abbreviations: ref = reference; ISUP = international society of urological pathology grading system for prostate cancer based on Gleason's score, GC = genomic classifier.

# Figure 1

A.



B.

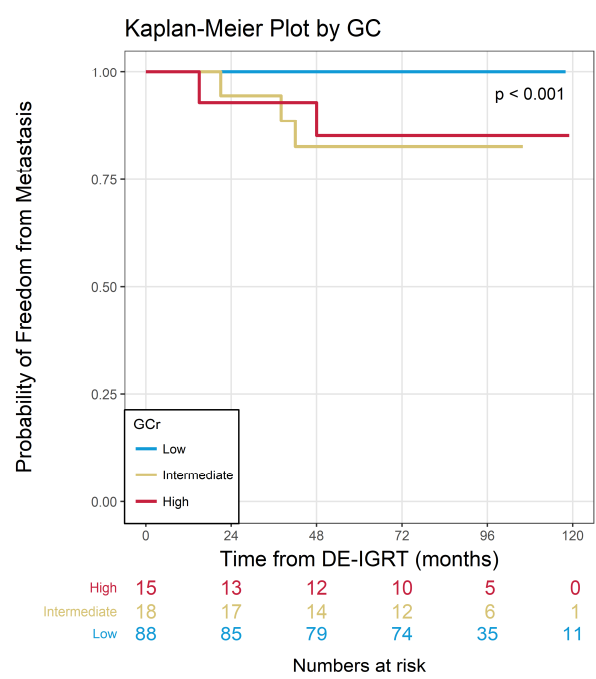
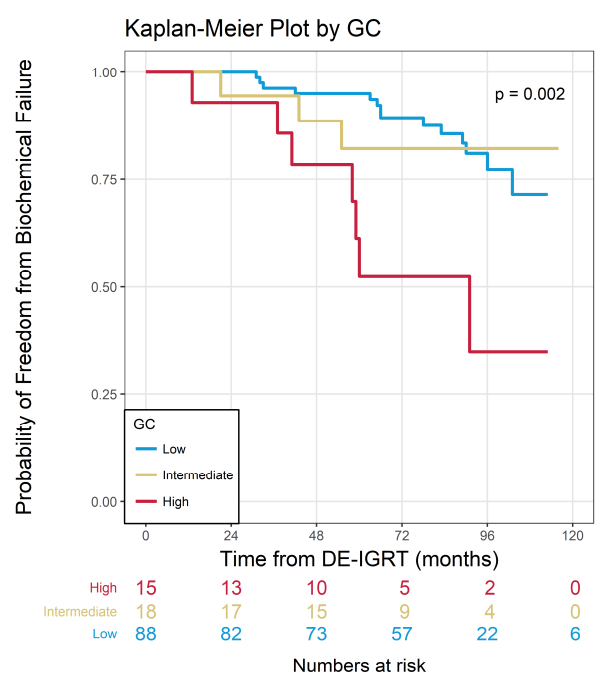


Figure 2

