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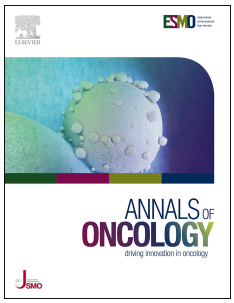

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Validation of the Decipher Genomic Classifier in Patients receiving Salvage Radiotherapy without Hormone Therapy after Radical Prostatectomy – An Ancillary Study of the SAKK 09/10 Randomized Clinical Trial

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Abstract

Background: The Decipher genomic classifier (GC) has shown to independently prognosticate outcomes in prostate cancer. The objective of this study was to validate the GC in a randomized phase 3 trial of dose-escalated salvage radiotherapy (SRT) after radical prostatectomy.

Patients and Methods: A clinical grade whole-transcriptome assay was performed on RP samples obtained from patients enrolled in SAKK 09/10, a phase 3 trial of 350 men with biochemical recurrence post-radical prostatectomy randomized to 64Gy vs. 70Gy without concurrent hormonal therapy or pelvic nodal radiotherapy (RT). A pre-specified statistical plan was developed to assess the impact of the GC on clinical outcomes. The primary endpoint was biochemical progression; secondary endpoints were clinical progression and time to hormone therapy. Multivariable analyses adjusted for age, T-category, Gleason score, post-radical prostatectomy persistent prostate-specific antigen (PSA), PSA at randomization, and randomization arm were conducted, accounting for competing risks.

Results: The analytic cohort of 226 patients was representative of the overall trial, with median follow-up of 6.3 years (IQR 6.1-7.2). GC (high vs. low-intermediate) was independently associated with biochemical progression (subdistribution hazard ratio [sHR] 2.26 [95% CI 1.42-3.60], $p<0.001$), clinical progression (HR 2.29 [95% CI 1.32-3.98], $p=0.003$), and use of hormone therapy (sHR 2.99 [95% CI 1.55-5.76], $p=0.001$). GC high patients had 5-year freedom from biochemical progression of 45% vs. 71% for GC low-intermediate. Dose escalation did not benefit the overall cohort, nor patients with lower vs. higher GC scores.

Conclusions: This study represents the first contemporary randomized controlled trial in patients treated with early SRT without concurrent hormone therapy or pelvic nodal RT that has validated the prognostic utility of the GC. Independent of standard clinicopathologic variables and RT dose, high-GC patients were more than twice as likely than lower-GC patients to experience biochemical and clinical progression and receive of salvage hormone therapy. This data confirms the clinical value of Decipher GC to personalize the use of concurrent systemic therapy in the postoperative salvage setting.

Keywords

Biomarkers, Decipher, prognosis, prostate cancer, salvage radiotherapy, postoperative radiotherapy

Highlights

- Decipher identifies patients at highest risk of progression who may require treatment intensification
- Decipher defines subgroups associated with improved outcomes when treated with very early SRT compared to late SRT
- Transcriptomic profiling can guide personalized management of SRT timing and the addition of systemic therapy

Introduction

More than 40% of intermediate- or high-risk prostate cancers are estimated to recur after radical prostatectomy, which suggests more than 30,000 men every year in the USA are diagnosed with biochemically recurrent disease.[1] Salvage radiotherapy (SRT) is currently the only potentially curative treatment for this patient population. Outcomes after SRT are heterogenous. However, conventional clinicopathologic factors (i.e., Gleason score, T-category, and prostate-specific antigen [PSA]), and even multivariable models (e.g., Tendulkar nomogram) are >25% of the time inaccurate in estimation of patient prognosis.[2] Therefore, differences in clinical outcomes highlight an intrinsic biological heterogeneity that is commonly underappreciated in clinical decision-making.

The Decipher genomic classifier (GC; Veracyte, Inc) is a commercial, tissue-based transcriptomic assay that was developed to aid in prostate cancer prognostication. It uses a machine-learning algorithm to summarize the expression of 22 genes into a risk score. A recent systematic review across 42 studies of the GC demonstrated that the GC improves prognostication and discrimination above and beyond clinicopathologic variables.[3] This includes the post-hoc analysis of the NRG/RTOG 9601 phase 3 clinical trial of SRT +/- hormonal therapy.[4]

The analysis plan and GC score generation for this current translational study of the Swiss Group for Clinical Cancer Research (SAKK) phase 3 randomized trial, SAKK 09/10, were completed prior to data-lock for the trial's primary endpoint analysis, making this the first study to pre-specify validation of the GC in advance of the trial's primary analysis. SAKK 09/10 is a unique trial, as it represents one of the only contemporary trials worldwide that used SRT alone without hormone

therapy or pelvic nodal radiotherapy. It compared the use of standard vs. dose-escalated SRT to the prostate bed and found no difference in any oncologic endpoint to date.[5] Thus, it was primarily hypothesized that the GC would predict biochemical progression after SRT, independent of conventional clinicopathological factors. Furthermore, it was hypothesized that the GC would independently stratify the risk of clinical progression and the initiation of salvage hormone therapy after SRT.

Methods

SAKK 09/10 trial and Translational Research

SAKK 09/10 (NCT01272050) is a prospective open-label, multicenter, randomized phase 3 trial testing whether dose-escalated SRT is superior to conventional dose SRT with respect to freedom from biochemical progression (FFBP). Three hundred and fifty patients with biochemical recurrence after radical prostatectomy were randomized to 64Gy (32 fractions, 2Gy/fraction) vs. 70Gy (35 fractions, 2Gy/fraction) to the prostate bed. Patients did not receive concomitant hormone therapy or pelvic nodal radiotherapy. Patients with evidence of biochemical recurrence after radical prostatectomy (two consecutive rises in PSA with final PSA >0.1 ng/mL, or 3 consecutive rises) and PSA at randomization ≤2 ng/mL were eligible. Further details on the inclusion and exclusion criteria can be found in **Supplementary Materials** or at ClinicalTrials.gov (NCT01272050).[5] The trial was sponsored by the SAKK with ethics committee approval at each of the 28 participating centers in Switzerland, Germany, and Belgium.

A translational research project was proposed primarily to study the prognostic performance of a biomarker on the patient samples in the SAKK 09/10 trial. Samples used for the GC analysis were

retrieved from the SAKK biobank and analyzed prior to the completion of the trial. A separate informed consent was signed by all patients who agreed on biobanking their tissue samples. Approval for this ancillary study was granted by the SAKK Board and Ethics Committee (Kantonale Ethikkommission Bern, KEK). Funding to support the costs of pathology review and for the genomic classifier testing was provided by Decipher Biosciences. The study followed PRoBE and REMARK criteria for prospective-blinded evaluation and analysis of a prognostic biomarker.[6,7]

Gene Expression Profiling and Decipher Genomic Classifier Scores

Tumor specimens were centrally reviewed and selected from the radical prostatectomy block with the index lesion (defined as the lesion with the highest-grade group and tumor volume) and were sampled using a 1.0 mm diameter punch tool. GC scores were generated using the clinical-grade, whole-transcriptome Decipher assay (San Diego, CA) as previously described on the punch sample.[4] GC scores were calculated based on the locked GC model and scores were generated on a scale of 0 to 1 (**Appendix**). The continuous GC scores were generated and then linked to the clinical trial database at the SAKK Statistics and Data Management Center. Locked categorical analyses used the validated low- (<0.45), intermediate- (0.45-0.60), and high- (>0.60) risk groups.[8] Due to the low number of samples in the study when analyzed by two arms and three GC risk groups, low- and intermediate-risk GC scores (≤0.60), which reported similar risks, were combined (as previously described).[9]

Study Objectives and Endpoints

The primary objective of this ancillary project was to study the independent association of the GC with the trial's original primary endpoint: time to FFBP. Similarly, the secondary objectives were to analyze the association of GC with secondary endpoints including time to clinical progression-free survival (PFS) and time to hormone therapy. All primary and secondary endpoints were defined per the trial protocol.

Events for FFBP were characterized by biochemical progression, defined as time from randomization to first occurrence of PSA rise (≥0.4ng/mL and greater than the previous PSA value), clinical recurrence (local, regional, and/or distant recurrence detected by imaging), or death due to clinical recurrence. Secondary endpoints included time to hormone therapy (from randomization) and clinical progression-free survival (events were characterized by clinical progression, defined as time from randomization to first record of clinical recurrence, start of hormone therapy, or death due to any cause).

Exploratory endpoints included rapid biochemical failure (rapid-BF; a binary event defined by PSA progression [≥0.4ng/mL] within 18 months), time to metastasis (defined as time from randomization to the first record of regional and/or distant recurrence), and metastasis-free survival (MFS; defined as time from randomization to the first record of regional and/or distant recurrence, or death of any cause). All analyses on exploratory endpoints were deemed to be exploratory and hypothesis-generating.

Statistical Analysis

A statistical analysis plan was pre-specified and approved by the SAKK Coordinating Center prior to data-lock for the SAKK 09/10 trial primary endpoint analysis; specifically, before clinical outcome data and trial results were available for analyses in this translational study. All patients with available samples were analyzed as randomized. A sample size justification was performed for the prognostic evaluation of GC for the primary endpoint, FFBP. Out of 350 patients enrolled in the trial, 272 patients had radical prostatectomy tissues available for transcriptomic profiling. A conservative failure rate of 20% sample-loss and a 40% estimated event rate, as per the original trial's assumptions, were assumed, resulting in an expected 217 samples yielding Decipher scores and 87 events. These assumptions provided 90% power to detect a hazard ratio of 1.2 per 0.1-unit increase in a univariable Cox regression model, using a two-sided alpha of 0.05. Therefore, the study was powered to validate GC as a prognostic classifier for FFBP. The power calculation was performed with an assumed Decipher standard deviation of 0.2.

All endpoints, except rapid-BF, were analyzed as time-to-event endpoints. FFBP was analyzed with death due to any cause without events or receipt of hormonal therapy as competing risks. Both time to metastasis and MFS were analyzed with local recurrence, receipt of hormone therapy, or death due to any cause without events (time to metastasis only) as competing risks, limited by how the data were collected in the trial. Details can be found in **Supplementary Table 1**. The event-free rates at given times within arms or GC risk groups were estimated by the cumulative incidence method and compared using Gray's test, when accounting for competing risks, or the log-rank test, otherwise.[10,11] To properly assess the association of GC with the time-to-event endpoints, univariable (UVA) and multivariable (MVA) survival analysis models were

constructed: Fine and Gray for FFBP, time to hormone therapy, time to metastasis, and MFS and Cox proportional hazards for clinical PFS.[12] Logistic regression models were constructed for rapid-BF. MVAs were adjusted for randomization arm, age, and most of the trial's stratification variables: Gleason score, pathological stage, post-radical prostatectomy PSA persistent status (defined as PSA between [0.1-0.4 ng/mL]), and PSA at randomization.

Subgroup analyses were performed with GC in addition to standard pre-SRT PSA cut points (0.2 ng/mL and 0.5 ng/mL) for all endpoints. Due to the low number of samples and events in the study when analyzed by two GC risk groups and three pre-SRT PSA groups, model-based estimates adjusting for GC risk group and pre-SRT PSA group were predicted from the appropriate models and 95% confidence intervals were constructed via bootstrapping.

Statistical analyses were performed using R (version 3.6.1) and SAS 9.4. All statistical tests were 2-sided and considered statistically significant at the 0.05 level. No adjustment for multiple testing was applied.

Results

Out of 350 patients enrolled in the trial, 233 patients had tissue available for genomic analysis (**Figure 1)**. Samples from 226 patients (97%) passed quality control and were included for final analysis (median age, 66 years [interquartile range (IQR) 62-70]). Median time from radical prostatectomy to randomization was 2.1 years (IQR 1.1-3.6) and median follow-up time for censored patients was 6.3 years (IQR 6.08-7.23). Median PSA at randomization was 0.3 ng/mL (IQR 0.2-0.53). The 64Gy (*n*=111) and 70Gy (*n*=115) arms were well balanced (**Table 1)** and

representative of the overall cohort (**Supplementary Table 2**). Similar treatment effects were observed for the full SAKK 09/10 cohort (*n*=344) and the GC analytic cohort (*n*=226) (**Supplementary Figure 1**). The distribution of GC scores between arms is shown in **Figure 2A**, with no significant differences in GC distribution between the 2 study arms. The median GC scores of each arm in the final cohort were similar: 0.36 (IQR 0.23-0.63) vs. 0.36 (IQR 0.2-0.59) for the 64Gy and 70Gy arms, respectively (Wilcoxon *p*=0.56). However, there were significant relationships between GC and other clinicopathologic variables, as expected. The GC score distribution by pathological T-stage, Gleason score, PSA persistence after radical prostatectomy, PSA at randomization, and EAU risk are shown in **Figures 2B-F**, respectively.

Decipher is Associated with Biochemical Progression

Higher GC was associated with a higher risk of biochemical progression. The GC was analyzed as both a continuous (scale, 0-1) and a categorical (binary) variable. As a continuous variable, the GC was significantly associated with biochemical progression, in both univariable (sHR 1.13 [95% CI 1.03-1.23], *p*=0.009) and multivariable analyses (sHR 1.14 [95% CI 1.04-1.25], *p*=0.006) (**Table 2**). Similar results were seen for categorical GC (high- vs. low-intermediate) in both univariable (sHR 2.21 [95% CI 1.41-3.47], *p*<0.001) and multivariable analyses (sHR 2.26 [95% CI 1.42-3.60], *p*<0.001) (**Table 2**). Patients with GC high had 5-year FFBP of 45% [95% CI 32-59] vs. 71% [95% CI 64-78] in GC low-intermediate (**Figure 3a**). Similar estimates were observed in the 64Gy vs. 70Gy arms within GC high (5-year FFBP of 51% [95% CI 32-70] vs. 39% [95% CI 20-59]) and within GC low-intermediate (75% [95% CI 65-84] vs. 69% [95% CI 59-78]) **(Supplementary Figure 2b-c; Supplementary Figure 5)**.

Decipher is Associated with Clinical Progression, Use of Hormonal Treatment, and Other Relevant Oncological Endpoints

Higher GC scores were independently associated with time to clinical progression-free survival (CPFS) and time to hormone therapy. In multivariable analyses, GC high vs. low-intermediate had an HR of 2.29 ([95% CI 1.32-3.98], *p*=0.003) for clinical progression and an sHR of 2.99 ([95% CI 1.55-5.76], *p*=0.001) for time to hormone therapy (**Supplementary Table 3**). Specifically, GC high had a 5-year freedom from hormonal treatment of 74% ([95% CI 61-86]) compared to 89% ([95% CI 84-94]) for GC low-intermediate (**Figure 3c**). The estimated probabilities of FFBP, CPFS, and freedom from hormone therapy according to low, intermediate, and high GC are shown in **Supplementary Figure 3.**

GC was prognostic for all endpoints, including exploratory endpoints, when evaluated both categorically and continuously (**Figure 4 and Supplementary Figure 4**). GC remained prognostic for biochemical progression in established clinical subgroups **(Supplementary Figure 5).** For example, GC (high vs. low-intermediate) was prognostic within Gleason score ≤ 7 tumors (sHR 2.16 [95% CI 1.30-3.58], *p*=0.003), pathological stage pT2-3a (sHR 1.97 [95% CI 1.18-3.29], *p*=0.009), undetectable and persistently elevated PSA post- radical prostatectomy (sHR 1.95 [95% CI 1.15-3.31], *p*=0.01 and sHR 5.31 [95% CI 1.76-16.01], *p*=0.003, respectively), and PSA at randomization >0.5 ng/mL (sHR 3.75 [95% CI 1.84-7.64], *p*<0.001). There were no significant interactions between GC score, clinical subgroup, and clinical endpoints.

Pre-SRT Subgroups

Pre-salvage RT PSA and the GC have been shown in NRG/RTOG 9601 to be valuable tools to personalize the use of hormone therapy with SRT, with those having higher pre-SRT PSAs and higher GCs deriving the most benefit from hormone therapy.[4] Given in SAKK 09/10 patients received SRT alone, outcomes by GC score in patients receiving late SRT (pre-SRT PSA >0.5 ng/mL, a stratification variable at randomization) were assessed. Late SRT was administered in 27% of patients (61/226), and the 5-year FFBP was 64% [95% CI 49-79] for GC low-intermediate compared to only 13% [95% CI 0-32] for GC high**.**

Similarly, for the time to hormone therapy endpoint, among the patients who received very early SRT with PSA <0.2 ng/mL, the 5-year hormonal treatment-free survival was 98% [95% CI 93-100] for GC low-intermediate and 88% [95% CI 63-100] for GC high. In contrast, for patients who received SRT with PSA >0.5 ng/mL, the 5-year hormonal treatment-free survival was 83% [95% CI 72-95] for GC low-intermediate compared to only 54% [95% CI 27-80] for GC high. In sensitivity analysis, categorical model-based estimates showed similar results to the empirical estimates for all endpoints (**Supplementary Table 4**).

Discussion

Herein, we confirm in a phase 3 randomized trial that there are heterogenous outcomes post-SRT, and that the GC adds independent prognostic performance to better identify men who are more or less likely to recur after SRT alone. Our results add to data from multiple other clinical trials of the Decipher GC demonstrating this tool can change clinical decision making (e.g., PRO-IMACT and G-MINOR) and identify those who will derive greater or lesser benefit from treatment intensification with hormone therapy.[13-16] In addition, there are ongoing phase 3 studies that

incorporate GC in different clinical scenarios and will shed further light on GC's role for better patient selection (E.g. NCT04513717, NCT05050084, NCT04484818). Our study represents level 1 data by the Simon et al. criteria for prognostic biomarkers, and to our knowledge, the Decipher GC is the only post-radical prostatectomy test to have this level of evidence.[17]

Through a pre-specified analysis of the SAKK 09/10 trial, it was hypothesized that the Decipher GC would be able to stratify patients with a significantly higher likelihood of PSA progression, clinical progression, and use of hormone therapy. Indeed, patients with high GC score tumors were more than twice as likely than patients with lower GC scores to experience PSA and clinical progression and receive salvage hormone therapy. In this contemporary trial, we observed a sample pass rate of 97% (similar to commercial testing pass rates), which reflects the overall better quality in the biological material obtained from SAKK 09/10 patients with an increased reliability in the genomic assessment.

Currently, clinicopathologic multivariable models (e.g., Tendulkar nomogram) have only modest performance to discriminate outcomes for men that receive SRT.[2] This makes it difficult to clinically decide which patients should or should not receive treatment intensification with hormone therapy or pelvic nodal radiotherapy. For this reason, in part, current AUA/ASTRO guidelines recommend all patients be offered treatment intensification with hormone therapy to SRT based on the overall survival benefit identified in NRG/RTOG 9601.[4,18] However, in this current study, only 65 patients experienced a clinical progression event during the study follow-up. Thus, the SOC recommendations to treat everyone with concurrent hormone therapy would, in theory, overtreat 71% of patients. In contrast, if treatment recommendations were guided solely

by Decipher (and not a more complex clinic-genomic model), only 33% of patients would potentially be over- or under-treated. Taking results from this study as an example, application of GC testing could decrease the absolute reduction in concurrent use of hormone therapy by 38%. In other words, 2.6 patients would need to be tested with GC (and provided care with GC-based treatment) to prevent 1 incorrect treatment decision: either withholding beneficial treatment or administering unnecessary hormonal treatment with SRT.

Routine treatment decisions made for men post-radical prostatectomy include the use of very early SRT (<0.2 ng/mL), early SRT (0.2-0.5 ng/mL), or late SRT (>0.5 ng/mL). This was confirmed in the current study as well; the 5-year FFBP was 80% [95% CI 69-91] for patients with pre-SRT PSA <0.2 ng/mL, compared to 65% [95% CI 57-74] for patients with pre-SRT PSA 0.2-0.5 ng/mL and 50% [95% CI 37-63] for patients with pre-SRT PSA >0.5 ng/mL. The use of GC can complement pre-SRT PSA and provide further risk stratification, allowing patients to make better informed treatment decisions around the timing of salvage treatment and/or adding hormone therapy. More specifically, for patients with lower GC scores, waiting to administer SRT until PSA rose to 0.2-0.5 ng/mL resulted in a decrease in 5-year FFBP rates of 11% (from 81% for very early to 70%), which for some patients, may not be considered a sufficient risk reduction to initiate salvage RT. Conversely, for patients with high GC, waiting too long to administer SRT resulted in a decrease in 5-year FFBP rates of 62% (from 75% for very early to 13% for late SRT). These results suggest that for GC high patients, intervening when the PSA burden is lowest results in improved outcomes. Furthermore, results from this study showed that patients with GC high and pre-salvage RT PSA >0.5 ng/mL have a nearly 90% risk of progression by 5 years, suggesting that knowledge of GC risk at radical prostatectomy and early referral for radiation oncology upon

initial PSA rise (especially for GC high) is critically important to delivering optimal care in this setting.

This study was based on a pre-specified analysis plan prior to data-lock of the parent randomized trial, but limitations are present. The sample size of the parent trial, and patients with available tissue, precluded additional subgroup analyses. Use of salvage hormone therapy was at the discretion of the treating physician, as in most trials, and was not based on strict pre-defined criteria. All interaction tests were non-significant, indicating that the GC had similar prognostic performance across all tested subgroups. However, the sample size and event rates preclude sufficient power to robustly rule out potential treatment effect differences.

Conclusion

This study represents the first contemporary randomized controlled trial in patients with recurrent prostate cancer treated with early SRT without concurrent hormone therapy or pelvic nodal radiotherapy that has validated the prognostic utility of the GC. Independent of standard clinicopathologic variables, patients with a high-GC were more than twice as likely than patients with a lower-GC to experience biochemical and clinical progression and receive salvage hormone therapy. Patients with high-GC have markedly improved outcomes when treated with very early SRT as compared to late SRT, and this data can help personalize the timing of SRT and use of concurrent hormone therapy in this patient population.

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Disclosures

V. Y. T. L., E.D, H-C.H, Y.L., and X.Z. are employees of Decipher Biosciences (Veracyte Inc.). D. J. S. T. is a contractor to Decipher Biosciences. All remaining authors have declared no conflicts of interest or funding declarations.

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Main Table Titles and Legends

Table 1 Demographic and clinical characteristics among the GC analytic cohort, Arm A patients, and Arm B patients.

Abbreviations: GC = genomic classifier; Gy = Gray; Q1, Q3 = the first and third quartile; WHO = World Health Organization; Op = operative; PSA = prostate-specific antigen; GG = grade group; RP = radical prostatectomy; EAU = European Association of Urology; GETUG = Genitourinary Group; RT = radiation therapy; 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy.

P-values were calculated using Wilcoxon rank sum test for continuous variables and Fisher's exact test or chi-squared test for categorical variables, as appropriate.

Table 2 GC performance for the prediction of biochemical progression in Fine and Gray models.

Abbreviations: Subdist. = Subdistribution; CI = confidence interval; GC = genomic classifier; Gy = Gray; PSA = prostate-specific antigen; Path. = Pathological.

Subdistribution Hazard Ratios of GC score were per 0.1-unit increase. Randomization arm was treated as a main effect in the models labelled univariable analyses, where applicable (arm effect not reported). Two patients with missing clinical data were dropped from the relevant models: one patient was missing pathological stage and one patient was missing pathological stage and Gleason score. Two patients with follow-up time = 0 were still included in analysis as per the trial's intent-to-treat principle.

** indicates p-values < 0.05*

Main Figure Titles and Legends

Figure 1 CONSORT diagram of the patient sample availability and sample quality from the SAKK 09/10–Decipher ancillary project

Abbreviations: Gy = Gray; QC = quality control; GC = genomic classifier.

Figure 2 GC distributions within clinical subgroups (A) for the GC analytic cohort and by treatment arm, (B) by pathological stage, (C) by Gleason score, (D) by persistent PSA after RP, (E) by PSA at randomization, and (F) by EAU risk.

Abbreviations: GC = genomic classifier; Gy = Gray; PSA = prostate-specific antigen; RP = radical prostatectomy; EAU = European Association of Urology.

Figure 3 Cumulative incidence estimates (1 – cumulative incidence) of GC Low-Intermediate- (≤0.60) and High- (>0.60) risk for (A) biochemical progression, (B) clinical progression, and (C) hormonal treatment.

Abbreviations: GC = Genomic Classifier; yrs = years; CI = confidence interval.

Cumulative incidence estimates (1 – cumulative incidence) were compared using Gray's test for biochemical progression and hormonal treatment and the log-rank test for clinical progression; estimates with 95% confidence intervals at 1, 3, and 5 years explicitly reported.

** indicates p-values < 0.05.*

Figure 4 Prognostic performance of GC risk group for all endpoints.

Abbreviations: Est. = estimate; GC = genomic classifier; Low-Int = Low-Intermediate; CI = confidence interval; mo = months; MFS = metastasis-free survival.

Number of patients, number of events, and 5-year event-free estimates are reported by GC risk group. Randomization arm was treated as a main effect in the Fine and Gray and Logistic models and as strata in the Cox proportional hazards model. Five-year event-free estimates and 95% confidence intervals were estimated by the cumulative incidence method, with the exception of rapid biochemical failure, which reports the event-free proportion. Effect sizes of GC are reported for each endpoint from the appropriate model (Fine and Gray for biochemical progression, hormonal treatment, metastasis, and metastasis or death (i.e., metastasis-free survival); Cox proportional hazards for clinical progression; and logistic for rapid biochemical failure). Two patients with follow-up time = 0 were still included in analysis as per the trial's intent-to-treat principle: one patient had follow-up time = 0 for all time-to-event endpoints and one patient had follow-up time = 0 for FFBP only.

** indicates p-values < 0.05; † indicates event-free proportion.*

Supplementary Table Titles and Legends

Supplementary Table 1 Definitions of events and competing risks for all study endpoints.

Abbreviations: w/in = within; mo = months; PSA = prostate-specific antigen; HT = hormonal therapy.

*Events are marked as "x" and competing risks are marked as "o". Metastasis and metastasis-free survival are defined by regional and/or distant recurrence via imaging, as defined by the trial variable "clinical progression type". Thus, local recurrence (denoted by +) and receipt of HT prior to the presence of recurrence (denoted by *) are treated as competing risks for the metastasis-related variables.*

Supplementary Table 2 Demographic and clinical characteristics in the full SAKK 09/10 trial cohort, the non-analytic cohort, and the GC cohort.

Abbreviations: GC = genomic classifier; Q1, Q3 = the first and third quartile; WHO = World Health Organization; Op = operative; PSA = prostate-specific antigen; GG = grade group; RP = radical prostatectomy; EAU = European Association of Urology; GETUG = Genitourinary Group; RT = radiation therapy; 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy.

P-values were calculated using Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables.

Supplementary Table 3 GC performance for the prediction of (A) Clinical Progression in Cox Proportional Hazards models and (B) receipt of Hormonal Treatment in Fine and Gray models.

Abbreviations: Subdist. = Subdistribution; CI = confidence interval; GC = genomic classifier; PSA = prostate-specific antigen; Path. = pathological.

(Subdistribution) Hazard Ratios of GC score were per 0.1-unit increase. Randomization arm was treated as a main effect in the Fine and Gray models (including the models labelled univariable analyses; arm effect not reported) and as strata in the Cox proportional hazards models. Two patients with missing clinical data were dropped from relevant models: one patient was missing pathological stage and one patient was missing pathological stage and Gleason score. One patient with follow-up time = 0 for clinical progression was still included in analysis as per the trial's intent-to-treat principle.

** indicates p-values < 0.05.*

Supplementary Table 4 Five-year event-free estimates with bootstrapped 95% confidence intervals within pre-salvage RT PSA subgroups (<0.2, 0.2-0.5, and >0.5 ng/mL) by GC risk group for all endpoints.

Abbreviations: PSA = prostate-specific antigen; GC = genomic classifier.

Empirical estimates and 95% confidence intervals were estimated by the cumulative incidence method, with the exception of rapid biochemical failure, which reports the event-free proportion. Model-based estimates were predicted from the appropriate model (Fine and Gray for FFBP, freedom from HT, freedom from metastasis, and MFS; Cox Proportional Hazards for clinical PFS; and logistic for rapid biochemical failure), adjusting for categorical Decipher and pre-SRT PSA group. The 95% confidence intervals were constructed via bootstrapping (B=1000).

Supplementary Figure Titles and Legends

Supplementary Figure 1 Cumulative incidence estimates (1 – cumulative incidence) for Arm A (64Gy) and Arm B (70Gy) for (A) biochemical progression, (B) clinical progression, and (C) hormonal treatment in the full SAKK 09/10 trial cohort and the GC analytic cohort.

Abbreviations: GC = genomic classifier.

Cumulative incidence estimates (1 – cumulative incidence) with 95% CI at 1, 3, and 5 years explicitly reported.

** indicates p-values < 0.05.*

Supplementary Figure 2 Cumulative incidence estimates (1 – cumulative incidence) of GC Low-Intermediate- (≤0.60) and High- (>0.60) risk in (A) the GC analytic cohort, (B) Arm A (64Gy), and (C) Arm B (70Gy) for biochemical progression.

Abbreviations: GC = genomic classifier; Gy = Gray; yrs = years; CI = confidence interval.

Cumulative incidence estimates (1 – cumulative incidence) were compared using Gray's test; estimates with 95% CI at 1, 3, and 5 years explicitly reported.

** indicates p-values < 0.05.*

Supplementary Figure 3 Cumulative incidence estimates (1 – cumulative incidence) of GC Low- (<0.45), Intermediate- (0.45-0.60), and High- (>0.60) risk for (A) biochemical progression, (B) clinical progression, and (C) hormonal treatment.

Abbreviations: GC = genomic classifier; yrs = years; CI = confidence interval.

Cumulative incidence estimates (1 – cumulative incidence) were compared using Gray's test for biochemical progression and hormonal treatment and the log-rank test for clinical progression; estimates with 95% CI at 1, 3, and 5 years explicitly reported.

** indicates p-values < 0.05.*

Supplementary Figure 4 Prognostic performance of GC score for all endpoints.

Abbreviations: GC = genomic classifier; CI = confidence interval; mo = months; MFS = metastasis-free survival.

Randomization arm was treated as a main effect in the Fine and Gray model and logistic model and as strata in the Cox proportional hazards model. Effect sizes of GC score were per 0.1-unit increased and are reported for each endpoint from the appropriate model (Fine and Gray for biochemical progression, hormonal treatment, metastasis, and metastasis or death (i.e., metastasis-free survival); Cox proportional hazards for clinical progression; and logistic for rapid biochemical failure). Two patients with follow-up time = 0 were still included in analysis as per the trial's intent-to-treat principle: one patient had follow-up time = 0 for all time-to-event endpoints and one patient had follow-up time = 0 for FFBP only.

** indicates p-values < 0.05.*

Supplementary Figure 5 Prognostic performance of GC risk groups within clinical subgroups for biochemical progression.

Abbreviations: Est. = estimate; GC = genomic classifier; Subdist. = Subdistribution; HR = Hazard Ratio; Low-Int = Low-Intermediate; CI = confidence interval; Gy = Gray; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

Number of patients, number of events, and 5-year event-free estimates are reported by GC risk group. Five-year event-free estimates and 95% confidence intervals were estimated by the cumulative incidence method. GC effect sizes are reported from the Fine and Gray model, where applicable. Two patients with missing clinical data were dropped from relevant models: one patient was missing pathological stage and one patient was missing pathological stage and

Gleason score. Two patients with follow-up time were still included in analysis as per the trial's intent-to-treat principle.

** indicates p-values < 0.05; ‡ indicates Cox proportional hazards model was used, due to no competing risks in the clinical subgroup.*

Supplementary Materials SAKK 09/10 Inclusion/Exclusion Criteria

Appendix Decipher algorithm

Table 1

Variables	GC Analytic Cohort	Arm A (64 Gy)	Arm B (70 Gy)	*p-value*
Total	226 (100.0)	111 (49.1)	115 (50.9)	
Age				
Median (Q1, Q3)	66 (62, 70)	66 (63, 71)	66 (62, 70)	0.515
WHO performance status				
0	213 (94.2)	107 (96.4)	106 (92.2)	0.254
1	13 (5.8)	4 (3.6)	9 (7.8)	
Pre-Op PSA				
Median (Q1, Q3)	8.05 (5.55, 12.1)	8.11 (5.47, 10.7)	7.83 (5.56, 13.3)	0.356
Positive surgical margins (%)				
Yes	113 (50.0)	57 (51.4)	56 (48.7)	0.734
Unavailable	3 (1.3)	2 (1.8)	1 (0.9)	
Extra-prostatic extension (%)				
Yes	105 (46.5)	49 (44.1)	56 (48.7)	0.624
Unavailable	1 (0.4)	1 (0.9)		
Seminal vesical invasion (%)				
Yes	28 (12.4)	13 (11.7)	15 (13.0)	0.920
Unavailable	2 (0.9)	1 (0.9)	1 (0.9)	
Lymphovascular invasion (%)				
Yes	29 (12.8)	12 (10.8)	17 (14.8)	0.504
Unavailable	1 (0.4)	1 (0.9)		
Lymphadenectomy type (%)				
Limited lymph node dissection	145 (64.2)	74 (66.7)	71 (61.7)	0.622
Extended lymph node dissection	51 (22.6)	22 (19.8)	29 (25.2)	
None	27 (11.9)	13 (11.7)	14 (12.2)	
Unavailable	3 (1.3)	2 (1.8)	1 (0.9)	
Pathological stage (%)				
pT2	120 (53.1)	61 (55.0)	59 (51.3)	0.854
pT3a	76 (33.6)	36 (32.4)	40 (34.8)	
pT3b	28 (12.4)	13 (11.7)	15 (13.0)	
Unavailable	2 (0.9)	1 (0.9)	1 (0.9)	
Pathological Gleason group (%)				
6 [GG1]	28 (12.4)	14 (12.6)	14 (12.2)	0.806

7 (3+4) [GG2]	94 (41.6)	46 (41.4)	48 (41.7)	
7 (4+3) [GG3]	71 (31.4)	36 (32.4)	35 (30.4)	
8 [GG4]	15 (6.6)	5 (4.5)	10 (8.7)	
9-10 [GG5]	17 (7.5)	9 (8.1)	8 (7.0)	
Unavailable	1 (0.4)	1 (0.9)		
Post-Op PSA				
Median (Q1, Q3)	0.04 (0.0142, 0.09)	0.04 (0.02, 0.09)	0.047 (0.01, 0.09)	0.941
Persistent PSA after RP (%)				
Undetectable (< 0.1 ng/mL)	175 (77.4)	85 (76.6)	90 (78.3)	0.886
Detectable (≥ 0.1 ng/mL)	51 (22.6)	26 (23.4)	25 (21.7)	
EAU High-risk (%)				
Yes	171 (75.7)	91 (82.0)	80 (69.6)	0.043
GETUG High-risk (%)				
Yes	179 (79.2)	90 (81.1)	89 (77.4)	0.604
PSA at randomization				
Median (Q1, Q3)	0.3 (0.2, 0.53)	0.3 (0.196, 0.53)	0.33 (0.2, 0.565)	0.362
PSA at randomization (%)				
≤ 0.5 ng/mL	165 (73.0)	82 (73.9)	83 (72.2)	0.890
> 0.5 ng/mL	61 (27.0)	29 (26.1)	32 (27.8)	
RT technique (%)				
3D-CRT	106 (46.9)	53 (47.7)	53 (46.1)	0.907
IMRT/Rotational	120 (53.1)	58 (52.3)	62 (53.9)	

Table 2

Model	Variable	Univariable		Multivariable	
		Subdist. Hazard Ratio (95% CI)	*P-value*	Subdist. Hazard Ratio (95% CI)	*P-value*
GC score	GC Score	1.13 (1.03 - 1.23)	0.009*	1.14 (1.04 - 1.25)	0.006*
	Arm B (70 Gy) vs Arm A (64 Gy)	1.38 (0.91 - 2.10)	0.13	1.29 (0.85 - 1.96)	0.24
	Age	0.94 (0.91 - 0.97)	<0.001*	0.93 (0.89 - 0.96)	<0.001*
	PSA at Randomization > 0.5 ng/mL vs <= 0.5 ng/mL	1.86 (1.19 - 2.91)	0.006*	2.60 (1.66 - 4.08)	<0.001*
	Path. Stage pT3b vs pT2-3a	1.75 (1.00 - 3.07)	0.05	1.12 (0.59 - 2.10)	0.73
	Gleason Score 8-10 vs <= 7	1.90 (1.14 - 3.19)	0.01*	1.55 (0.88 - 2.71)	0.13
	Persistent PSA Detectable vs Undetectable	0.64 (0.36 - 1.14)	0.13	0.53 (0.31 - 0.92)	0.02*
GC risk group	GC High vs Low-Intermediate	2.21 (1.41 - 3.47)	<0.001*	2.26 (1.42 - 3.60)	<0.001*
	Arm B (70 Gy) vs Arm A (64 Gy)	-	-	1.28 (0.84 - 1.94)	0.25
	Age	-	-	0.93 (0.90 - 0.97)	<0.001*
	PSA at Randomization > 0.5 ng/mL vs <= 0.5 ng/mL	-	-	2.54 (1.63 - 3.98)	<0.001*
	Path. Stage pT3b vs pT2-3a	-	-	1.30 (0.72 - 2.33)	0.39
	Gleason Score 8-10 vs <= 7	-	-	1.49 (0.83 - 2.67)	0.18
	Persistent PSA Detectable vs Undetectable	-	-	0.53 (0.30 - 0.92)	0.02*

Figure 1

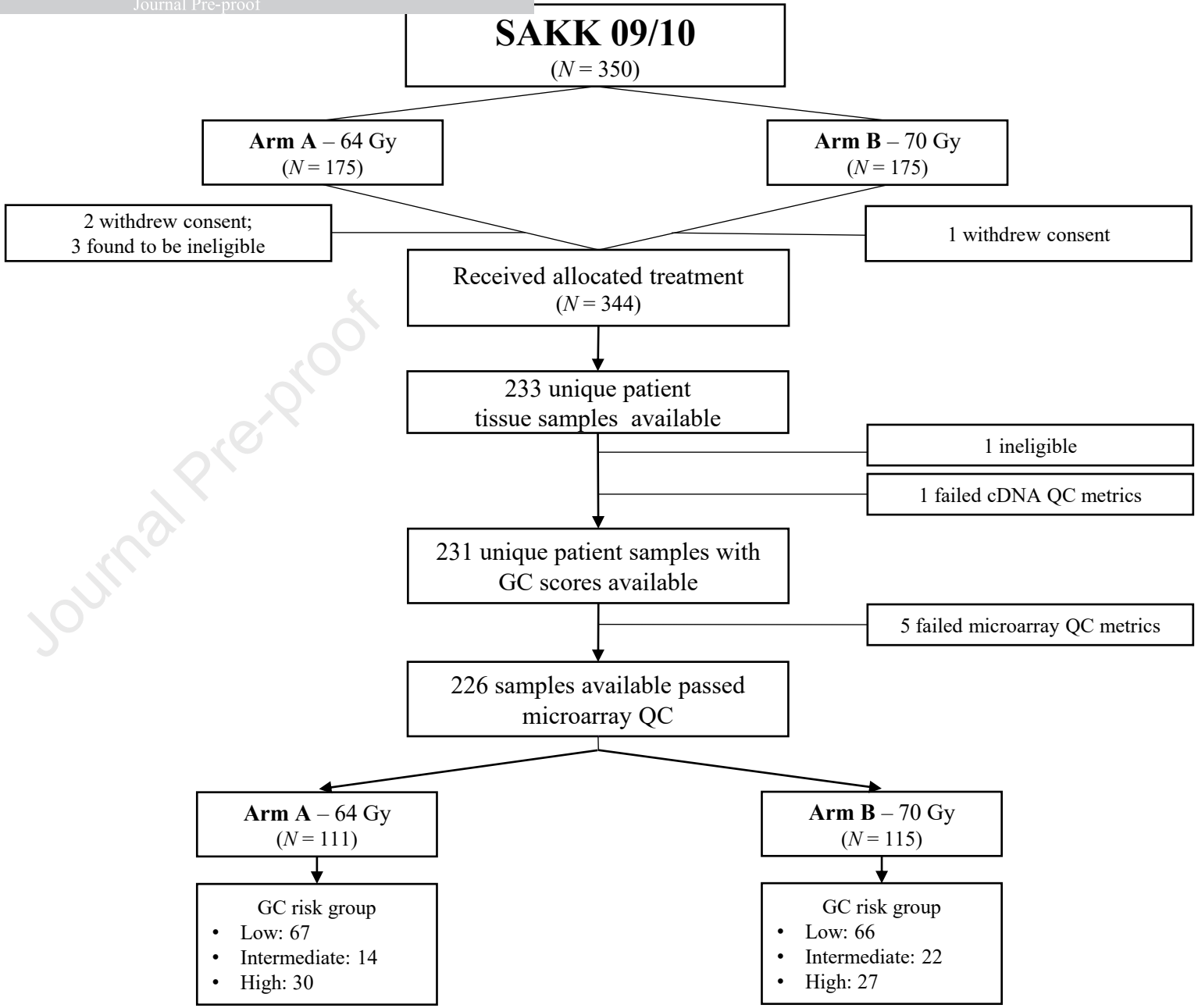


Figure 2

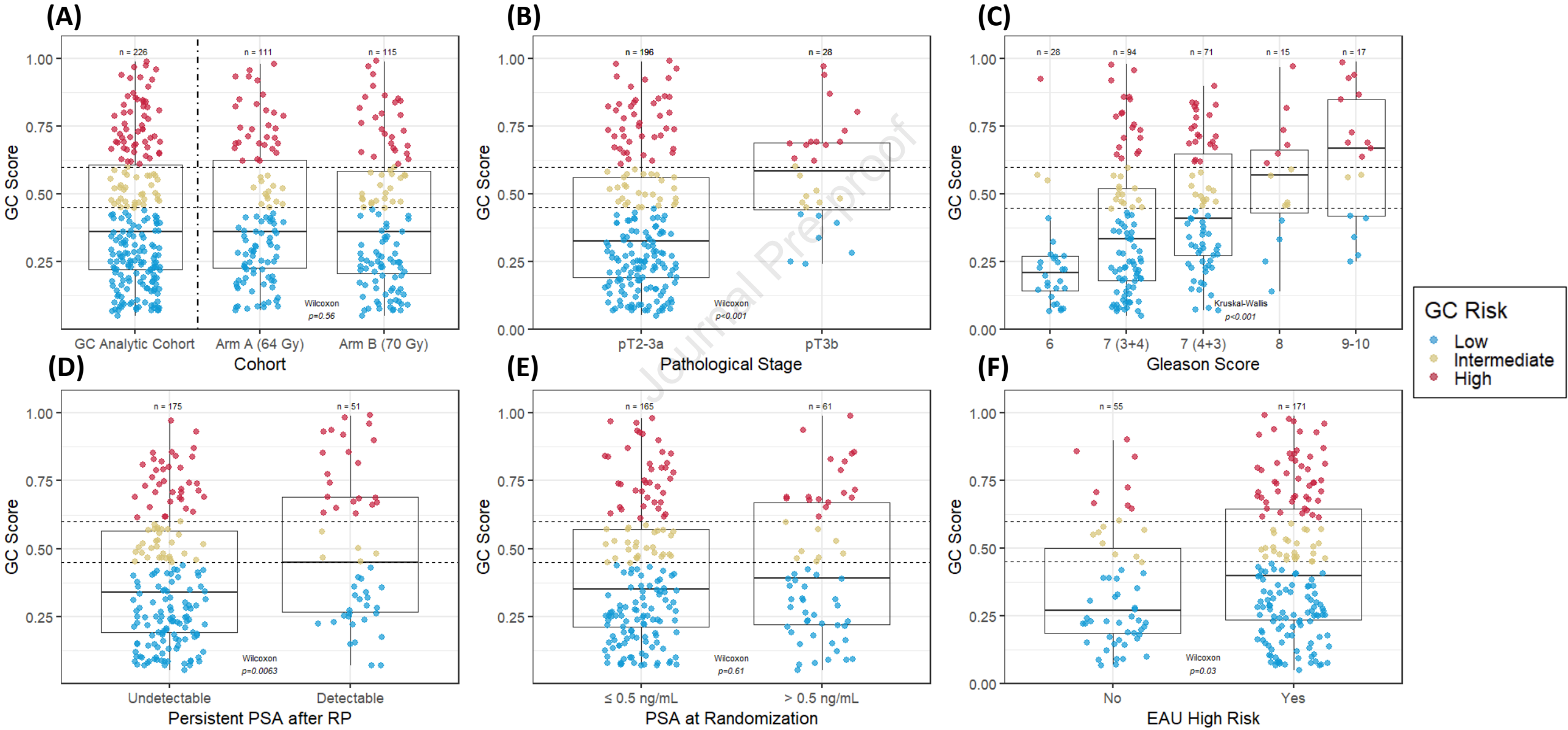
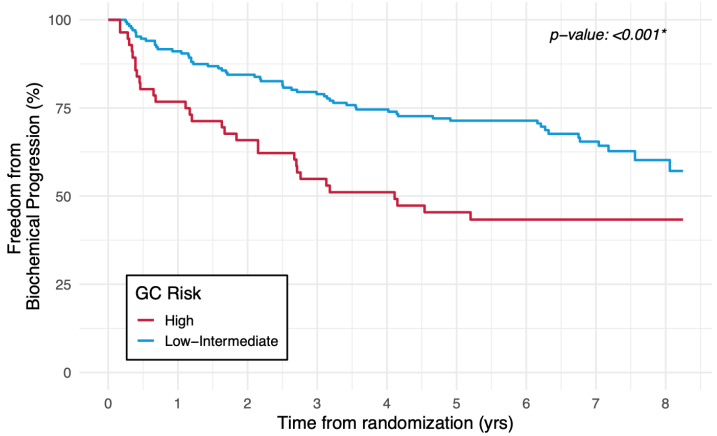


Figure 3

(A)



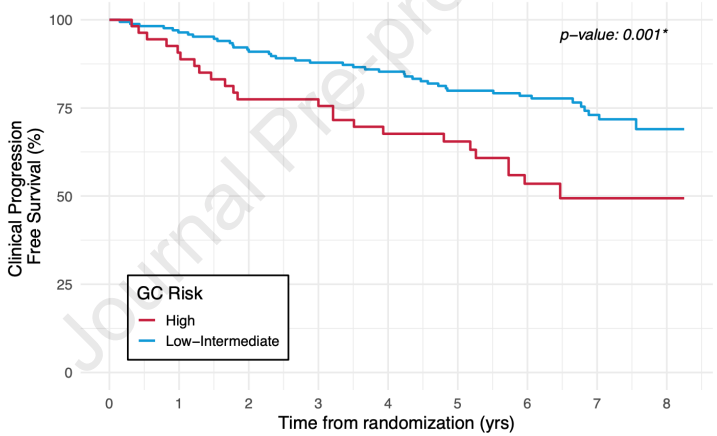
High	56	(2)	36	(2)	27	(3)	19	(18)	2
Low–Intermediate	168	(3)	138	(7)	116	(17)	100	(63)	18

Patients at risk (censored)

High	77% (66%–88%)	55% (42%–68%)	45% (32%–59%)
Low–Intermediate	91% (87%–95%)	79% (73%–85%)	71% (64%–78%)

Event–free rate (95% CI)

(B)



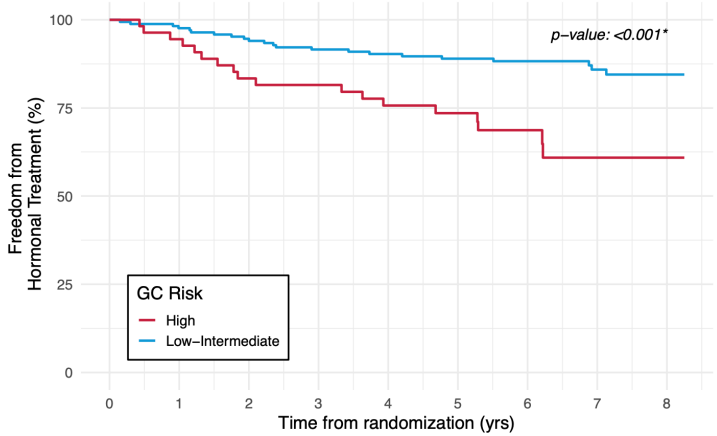
High	57	(4)	41	(4)	34	(9)	22	(25)	2
Low–Intermediate	168	(2)	149	(7)	132	(20)	107	(70)	19

Patients at risk (censored)

High	91% (83%–99%)	76% (64%–87%)	65% (52%–79%)
Low–Intermediate	96% (94%–99%)	88% (83%–93%)	80% (74%–86%)

Event–free rate (95% CI)

(C)



High	57	(3)	45	(3)	39	(10)	27	(31)	2
Low–Intermediate	169	(2)	155	(6)	138	(25)	115	(81)	20

Patients at risk (censored)

High	95% (88%–100%)	82% (71%–92%)	74% (61%–86%)
Low–Intermediate	98% (95%–100%)	92% (87%–96%)	89% (84%–94%)

Event–free rate (95% CI)

Figure 4

	N (event)			5-year Event-Free Est.			GC Risk Group	Effect Size	
	GC Analytic Cohort	GC Low-Int	GC High	GC Analytic Cohort	GC Low-Int	GC High	(High vs Low-Intermediate)	(95% CI)	*p-value*
Biochemical Progression	226 (88)	169 (57)	57 (31)	65% (58%-71%)	71% (64%-78%)	45% (32%-59%)		2.21 (1.41 - 3.47)	<0.001*
Clinical Progression	226 (65)	169 (41)	57 (24)	76% (71%-82%)	80% (74%-86%)	65% (52%-79%)		2.26 (1.36 - 3.75)	0.002*
Rapid Biochemical Failure (≤ 18 mo)	226 (38)	169 (22)	57 (16)	83%†	87%†	72%†		2.70 (1.29 - 5.65)	0.008*
Hormonal Treatment	226 (40)	169 (22)	57 (18)	85% (80%-90%)	89% (84%-94%)	74% (61%-86%)		3.05 (1.64 - 5.69)	<0.001*
Metastasis	226 (38)	169 (21)	57 (17)	86% (81%-90%)	89% (84%-94%)	75% (63%-87%)		2.96 (1.57 - 5.59)	<0.001*
Metastasis or Death (MFS)	226 (47)	169 (28)	57 (19)	83% (77%-88%)	85% (79%-91%)	75% (63%-87%)		2.47 (1.39 - 4.41)	0.002*