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Radiographic progression-free survival as a surrogate endpoint for overall survival in chemotherapy-naïve metastatic castration-resistant prostate cancer: a correlation meta-analysis

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Introduction

- Prostate cancer is the second most common cancer among men.[1] The 5-year relative survival rate for metastatic prostate cancer is 30%.[2]
- Most men will eventually experience disease progression despite traditional androgen-deprivation therapy, in which case the disease is termed castration-resistant or castration-recurrent prostate cancer (CRPC)[3]
- Overall survival (OS) is generally the gold standard endpoint for the evaluation of oncology trials
- However, observing a benefit in OS may require considerably long follow-up time
- Therefore, establishing intermediate endpoints such as radiographic progression-free survival (rPFS) as surrogates for OS may expedite the development of new treatments for prostate cancer, increase statistical power during clinical trial design and enable earlier assessment of RCTs conducted in metastatic CRPC (mCRPC)
- Prior research has been conducted to assess the validity of rPFS in prostate cancer patients
  - Halabi et al (2021)[4] assessed rPFS as a surrogate endpoint for OS in mCRPC patients majority of which were chemotherapy-naïve
    - Only correlation from weighted linear regression modelling was assessed
    - No cross-validation was performed to investigate the robustness of the model
    - The association between the treatment effects on rPFS and OS did not meet their pre-specified threshold for valid surrogacy
  - Gharzai et al (2022)[5] investigated multiple surrogate endpoints (biochemical-failure [BF], clinical failure, BF-free survival, progression-free survival, and rPFS) in metastatic prostate cancer
    - The patient population included both castration sensitive or resistant patients
    - rPFS-OS association was not investigated for mCRPC patients
    - The authors concluded that commonly used clinical endpoints were not valid surrogate endpoints for OS
- Although rPFS-OS association was previously assessed broadly in metastatic prostate cancer, little research has been done to assess this relationship among chemotherapy-naïve mCRPC patients

Objective

- To evaluate the appropriateness of rPFS as a surrogate for OS in adults with mCRPC who progressed after one to two second generation hormonal therapies in pre-chemotherapy setting

Methods

Targeted literature review and evidence base

- A targeted literature review was conducted using adapted standard methodologies for conducting systematic reviews[6]
- MEDLINE® and Embase were searched from database inception to December 14, 2021. Searches were limited to the English language.
- Search included articles from randomized controlled trials (RCTs) of adults with chemotherapy-naïve mCRPC who progressed after one to two second generation hormonal therapies and received any second-generation nonsteroidal anti-androgen therapies
- Outcomes of interest were OS and rPFS or its analogues including bone progression-free survival and tumor progression-free survival
- To be included in the evidence base, for each endpoint, RCTs must have reported relative treatment effects for both OS and rPFS either in the form of hazard ratios (HRs) or Kaplan-Meier (KM) curves from each arm
- For trials that reported KM curves only, pseudo individual patient-level data were generated using the Guyot algorithm from which the HRs were subsequently calculated using the Cox proportional hazards model[7]

Data analysis

Trial-level surrogacy models and analysis sets

- The surrogacy of rPFS for OS at the trial-level was assessed using two meta-analysis models
- HRs were log-transformed to be consistent with the linearity assumption for the relationship between the treatment effects
- The first model was based on an alternative bivariate random-effects meta-analysis (BRMA) model proposed by Riley et al (2008),[8] which does not require the knowledge of within-study correlation[9] and provides an overall correlation measure between the log-transformed HRs of rPFS and OS (i.e., log-HR_{rPFS} and log-HR_{OS}). This is an advantage as most published studies do not report within-study correlations.
- The second model was a weighted linear regression (WLR) where the inputs from each trial were weighted by their corresponding sample size. The association between log-HR_{rPFS} and log-HR_{OS} was measured by the Pearson correlation coefficient
- To test the strength of the results in sub-settings, five separate sensitivity analyses were conducted by omitting:
  - 1. Trials failing the proportional hazards assumption
  - 2. Trials that either did not specify the events or include death in their rPFS evaluations
  - 3. One trial with mismatched index dates between rPFS and OS
  - 4. Trials that permitted treatment crossover
  - 5. Trials that did not report HR but KM curves for at least one endpoint

Assessing the correlation estimates from BRMA and WLR

- The German Institute of Quality and Efficiency in Health Care (IQWiG) guidelines were used to assess the strength of the correlation estimate from both models[10]
- According to the IQWiG criteria, a correlation is classified as strong if the lower limit of its 95% confidence interval (CI) is ≥ 0.85, weak if the upper limit of its 95% CI is ≤ 0.7, and moderate otherwise
- The validity of the WLR model was assessed by using leave-one-out cross-validation (LOOCV)
- Prediction accuracies on the statistical significance of HR_{OS} (at a default 95% confidence level) were also reported for each analysis
- To assess the validity of WLR, results of LOOCV were evaluated according to the National Institute for Health and Care Excellence (NICE) Decision Support Unit Technical Support Document 20[9]

Results

Study selection

- Of 9,885 records identified, 24 publications pertaining to 23 unique RCTs were included in the literature review and subsequent correlation meta-analysis (**Figure 1**)
- A list of trials included in each analysis set is provided in **Table 1**

Figure 1. PRISMA flow diagram

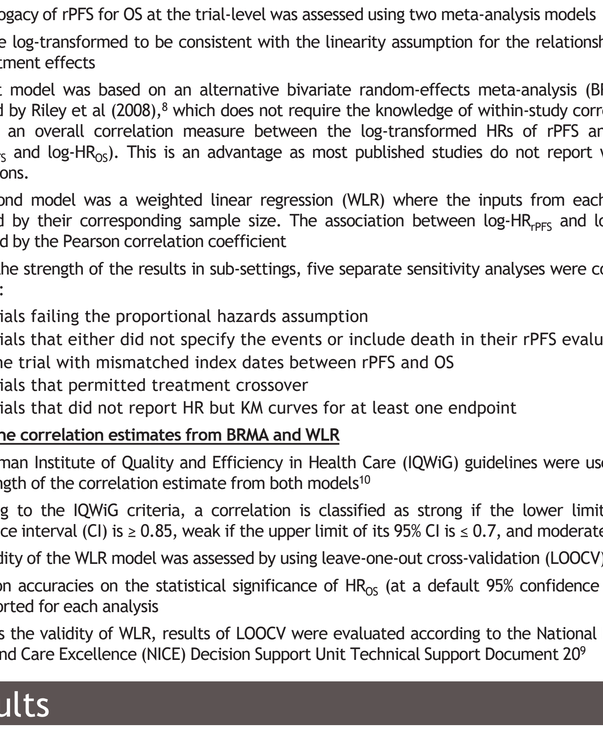
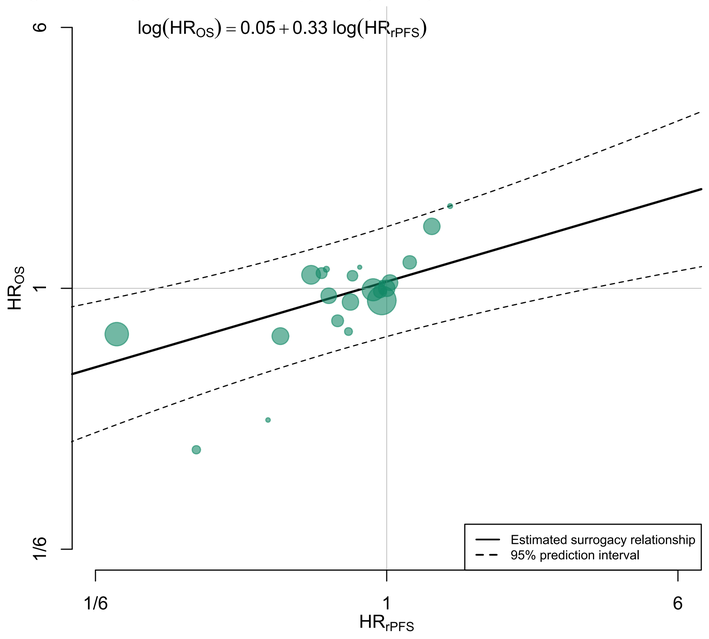


Table 1. List of included/excluded in each analysis set

Analysis	n	
Primary analysis		
Full analysis set	23	**Included studies:** PREVAIL-ASIA (2022), READY (2013), CABADOC (2021), PREVAIL (2014), Beer et al (2017), PON-PC-02 (2021), PRINCE (2018), ENTHUSE (2013), PROSTY (2013), CALGB 90401 (2012), NePro (2012), FIRSTANA (2017), Pan et al (2014), STAMPEDE (2018), CURTAXEL (2021), Petrioli et al (2011), SWOG 9916 (2004), MAINSAIL (2015), SWOG S0421 (2013), COU-AA-302 (2015), ACIS (2021), ERA 223 (2019), TASQUINIMOD (2016)
Sensitivity analyses		
1) Excluding trials that failed the proportional hazards assumption	13	**Studies omitted from the full analysis set:** SWOG 9916 (2004), CALGB 90401 (2012), NePro (2012), READY (2013), PREVAIL (2014), COU-AA-302 (2015), Beer et al (2017), PRINCE (2018), STAMPEDE (2018), CURTAXEL (2021)
2) Excluding trials that either did not report event type or did not include death in the definition of radiographic progression-free survival	14	**Studies omitted from the full analysis set:** NePro (2012), ENTHUSE (2013), READY (2013), Pan et al (2014), FIRSTANA (2017), PRINCE (2018), CABADOC (2021), CURTAXEL (2021), PON-PC-02 (2021)
3) Excluding one trial with mismatched index dates between rPFS and OS	22	**Studies omitted from the full analysis set:** Pan et al (2014)
4) Excluding trials that permitted crossover	21	**Studies omitted from the full analysis set:** COU-AA-302 (2015), CABADOC (2021)
5) Excluding trials that did not report HR but KM-plots for at least one endpoint	18	**Studies omitted from the full analysis set:** SWOG 9916 (2004), Petrioli et al (2011), Pan et al (2014), CABADOC (2021), CURTAXEL (2021)

n – number of treatment effect comparisons

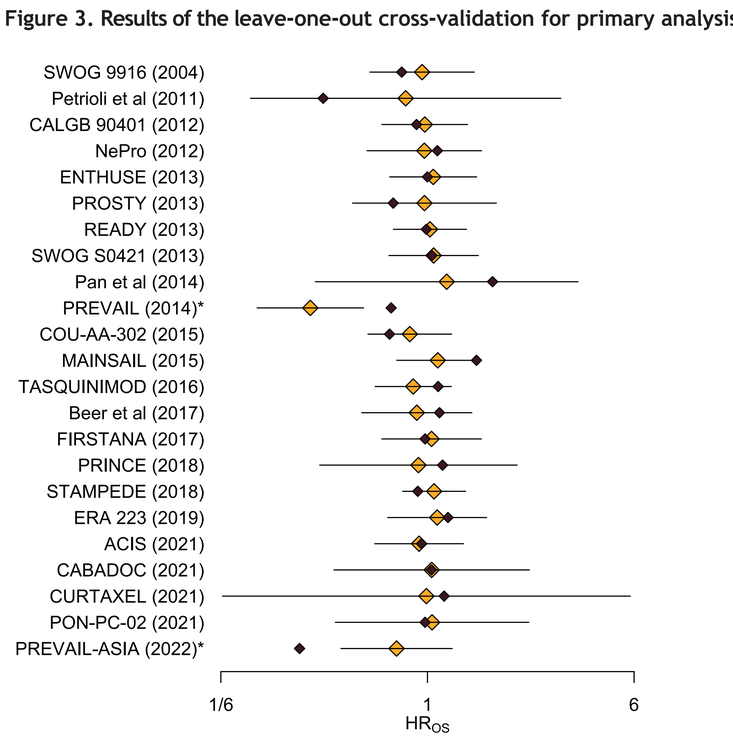
Figure 2. Regression plot for primary analysis



Legend: The predictive surrogacy equation is graphed as a solid straight line with its corresponding 95% predictive interval boundaries as dashed curved lines. Green circles in the plot represent relative treatment effects from the RCTs in the evidence base and their sizes represent their relative weights (i.e. sample sizes) in the WLR_τ.

Abbreviations: HR – hazard ratio; OS – overall survival; rPFS – radiographic progression-free survival

Figure 3. Results of the leave-one-out cross-validation for primary analysis



Legend: The brown and yellow diamonds are the reported and the predicted HR_{OS} measures, respectively. Corresponding to the predicted HR_{OS} measures, the 95% PIs are presented as black horizontal lines. To assess the cross-validation results, reported HR_{OS} measures were compared against their corresponding 95% PIs. Comparisons in which the 95% PI did not cover the reported HR_{OS} are marked with an asterisk (*).

Abbreviations: HR – hazard ratio; OS – overall survival

Full analysis set

- The surrogacy equation was $\log(HR_{OS}) = 0.05 + 0.33 \times \log(HR_{rPFS})$
- Using LOOCV, in two out of 23 (8.7%) comparisons, reported HR_{OS} laid outside of their 95% prediction intervals (PIs)
- Results from the WLR model and LOOCV on the full analysis set are presented in **Figure 2** and **Figure 3**, respectively

Sensitivity analysis (1) excluding trials that failed the proportional hazards assumption

- The surrogacy equation was $\log(HR_{OS}) = 0.12 + 0.76 \times \log(HR_{rPFS})$
- Using LOOCV, in one out of 13 (7.7%) comparisons, reported HR_{OS} laid outside of its 95% PI

Sensitivity analysis (2) excluding trials that either did not specify the events or include death in their rPFS evaluations

- The surrogacy equation was $\log(HR_{OS}) = 0.05 + 0.33 \times \log(HR_{rPFS})$
- Using LOOCV, in two out of 14 (14.3%) comparisons, reported HR_{OS} laid outside of their 95% PIs

Sensitivity analysis (3) excluding one trial with mismatched index dates between rPFS and OS

- The surrogacy equation was $\log(HR_{OS}) = 0.04 + 0.32 \times \log(HR_{rPFS})$
- Using LOOCV, in two out of 22 (9.1%) comparisons, reported HR_{OS} laid outside of their 95% PIs

Sensitivity analysis (4) excluding trials that permitted crossover

- The surrogacy equation was $\log(HR_{OS}) = 0.05 + 0.31 \times \log(HR_{rPFS})$
- Using LOOCV, in two out of 21 (9.5%) comparisons, reported HR_{OS} laid outside of their 95% PIs

Sensitivity analysis (5) excluding trials that did not report HR but KM-plots for at least one endpoint

- The surrogacy equation was $\log(HR_{OS}) = 0.05 + 0.32 \times \log(HR_{rPFS})$
- Using LOOCV, in two out of 18 (11.1%) comparisons, reported OS HRs laid outside of their 95% PIs

A summary of the results of all analyses is presented in **Table 2**

Table 2. Summary of analysis results

Analysis	n	R_{BRMA} (95% CI)	R_{WLR} (95% CI)	Correlation strength	LOOCV (% Validated)	Prediction Accuracy for HR_{OS} significance
Primary analysis						
Full analysis set	23	0.67 (0.41, 0.82)	0.66 (0.46, 0.90)	Both moderate	21/23 (91.3%)	16/23 (69.6%)
Sensitivity analyses						
1) Excluding trials that failed the proportional hazards assumption	13	0.88 (0.61, 0.97)	0.82 (0.25, 1.00)	Both moderate	12/13 (92.3%)	7/13 (53.8%)
2) Excluding trials that did not specify the events or include death in their rPFS evaluations	14	0.63 (0.26, 0.84)	0.66 (0.45, 0.92)	Both moderate	12/14 (85.7%)	8/14 (57.1%)
3) Excluding one trial with mismatched index dates between rPFS and OS	22	0.64 (0.37, 0.81)	0.66 (0.42, 0.90)	Both moderate	20/22 (90.9%)	16/22 (72.7%)
4) Excluding trials permitting treatment crossover	21	0.64 (0.37, 0.81)	0.65 (0.31, 0.91)	Both moderate	19/21 (90.5%)	15/21 (71.4%)
5) Excluding trials that did not report HR but KM-plots for at least one endpoint	18	0.67 (0.38, 0.84)	0.67 (0.38, 0.90)	Both moderate	16/18 (88.9%)	14/18 (77.8%)

Note: Accuracy is defined as the proportion of the HR_{OS} significance correctly predicted by the model, out of all predicted HR_{OS}. Correlation strength was based on the IQWiG criteria.

Abbreviations: BRMA – bivariate random-effects meta-analysis; CI – confidence interval; HR – hazard ratio; IQWiG – Institute for Quality and Efficiency in Health Care; LOOCV – leave-one-out cross-validation; n – number of treatment effect comparisons; OS – overall survival, R_{BRMA} – Pearson correlation estimate based on BRMA; rPFS – radiographic progression-free survival; R_{WLR} – Pearson correlation estimate based on WLR, WLR – weighted linear regression

Conclusions

- According to IQWiG recommendations, results suggest a moderate positive correlation between rPFS and OS across all analyses in adults with chemotherapy-naïve mCRPC who progressed after one to two second generation hormonal therapies
- Alignment rates between the reported OS HRs and their 95% PIs were high during LOOCV, ranging from 85-90%, albeit none of the analyses met NICE's recommendation of ≥95% coverage for validity
- It was observed that restricting the evidence base to trials meeting the proportional hazards assumption led to stronger correlation estimates

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