HTA91

Correlation of Intermediate Clinical Endpoints for Overall Survival in Localized or Locally Advanced Prostate Cancer: Analysis of Individual Real-World Data

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Key Takeaways

Our findings of moderate strength correlations between rwEFS-rwOS and rwNED-rwOS from individual-level RWD suggest that EFS and NED could potentially be meaningful ICEs for OS in patients with LPC/LAPC

Strong strength of rwMFS-rwOS correlation from individual-level RWD reinforces MFS as a clinically meaningful ICE for LPC, concordant with existing evidence[2,3]

Conclusions

Our findings are consistent with a correlation analysis of ICEs for OS in patients with high-risk LPC/LAPC using data from randomized and nonrandomized studies[6]

Strengths of our study include the large sample size and the use of individual-level RWD, which helps to avoid aggregation bias associated with summary-level data

Moreover, our study was conducted across 4 different real-world datasets and demonstrates consistency of findings across multiple data sources from the US and the UK

A limitation of our study is the insufficient information from Optum databases to confirm high-risk status of patients with LPC/LAPC. In addition, real-world surrogates for ICEs were not as precise as the systematic collection of actual events in clinical trials

Overall, findings from correlation analyses could have significant implications for clinical trial design, regulatory and health technology assessment considerations, and patient care

Acknowledgments

Writing assistance was provided by Ann Tighe, PhD, of Parexel. The study was sponsored by Johnson & Johnson.

Disclosures

Dr Jahn has nothing to disclose.

Introduction

- Overall survival (OS) and metastasis-free survival (MFS) based on conventional imaging are established endpoints in nonmetastatic prostate cancer (PC)[1,2]
- MFS has been validated as a strong surrogate endpoint for OS in patients with high-risk localized PC (LPC)[2,3]
- The use of OS and MFS as study endpoints in early disease settings, such as LPC and locally advanced PC (LAPC), is limited by the extended time until metastasis and death and by noncancer deaths precluding cancer-related OS and MFS events[4]
- These limitations have led to investigation of intermediate clinical endpoints (ICEs), including event-free survival (EFS) and no evidence of disease (NED), as potential surrogates for OS[4-6]

Objective

- The primary objective of our study was to use individual-level real-world data (RWD) to explore correlations between ICEs (rwMFS, rwEFS, rwNED) and rwOS in patients with LPC/LAPC

Methods

- RWD from the US (ConcertAI RWD360® claims and electronic health records [EHR]; Optum Claims; Optum EHR) and UK (Clinical Practice Research Datalink [CPRD] EHR) were analyzed separately (Table 1)
- Patients with LPC/LAPC who underwent radical prostatectomy (RP) prior to any progression to metastatic or castration-resistant PC were eligible for inclusion in the study. ICE definitions are shown in Table 2
- The study period, defined as the time encompassing all the claims and EHR data, ranged from January 2010 to December 2024. The index date was defined as the date of RP to treat LPC/LAPC
- Correlation analyses between ICEs and rwOS were estimated with Kendall's tau and parametric statistical models developed by Fleischer et al.[7]; bootstrapping to validate sample statistics was performed
- Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for landmark analyses of rwOS according to ICE landmark-event status (rwEFS and rwNED) at 3, 4, and 5 years post index

Table 1: Real-world databases used in study

Database	Type of data	Inclusion period
ConcertAI (US)	Electronic health records (EHR) and claims-based information, data are linked across multiple sources	2010-2024[a]
Optum Claims (US)	Commercial claims patients (aged 0-65 years) with some Medicare	2011-2023[b]
Optum EHR (US)	EHR	2011-2023[b]
CPRD (UK)	EHR from primary care practices (linked to cancer registry and other secondary data)	2010-2024[b]

[a]≥1 year pre-index (date of earliest activity in medical record to index date).
[b]≥1 year lookback period.

Table 2: ICE definitions

ICE	Definition[a]
MFS	Index: Date of radical prostatectomy (RP) Events: Earliest date of metastasis, mortality
EFS	Index: Date of RP Events: Earliest event out of date of metastasis, CRPC, mortality, or BCR
NED	Index: Date of RP Events: Earliest event out of nmCRPC, mCSPC, mCRPC, BCR, or mortality

BCR, biochemical recurrence; CRPC, castration-resistant prostate cancer; ICE, intermediate clinical endpoint; mCSPC, metastatic castration-sensitive prostate cancer; mCRPC, metastatic CRPC; nmCRPC, nonmetastatic CRPC.
[a]ICEs censored at last activity.

Results

- A total of 3978 (ConcertAI), 28,530 (Optum Claims), 34,653 (Optum EHR), and 6894 (CPRD) patients were included (Table 3). Median age and median follow-up ranged from 64 to 65 years and from 34 to 63 months, respectively, across databases

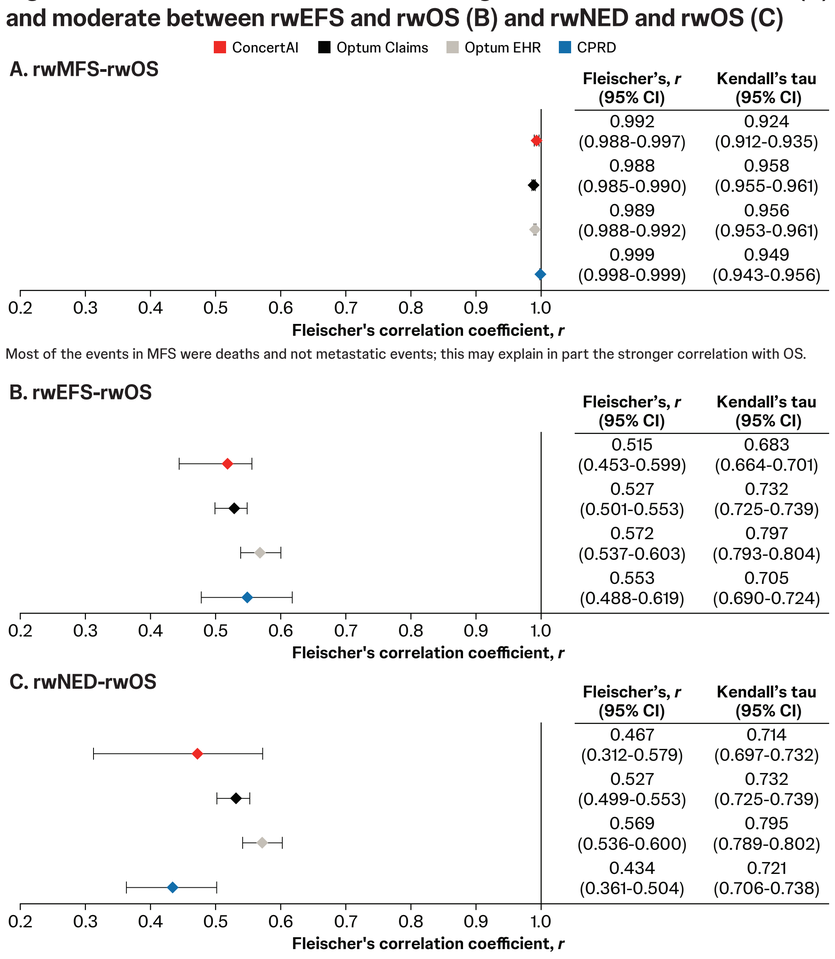
Table 3: Patient data at baseline

ICE	ConcertAI N=3978	Optum Claims N=28,530	Optum EHR N=34,653	CPRD N=6894
Age at index, years				
Mean (SD)	63.0 (6.7)	64.3 (7.5)	63.2 (7.0)	63.4 (6.8)
Median (IQR)	63.8 (58.4-68.0)	65.0 (59.0-70.0)	64.0 (58.0-68.0)	64.0 (59.0-69.0)
Time from PC diagnosis to index, mos				
Mean (SD)	5.3 (11.7)	2.6 (1.2)	1.9 (1.3)	4.7 (9.0)
Median (IQR)	2.3 (1.3-4.0)	2.4 (1.7-3.3)	1.7 (0.9-2.6)	2.7 (1.9-3.9)
Duration of follow up, mos				
Median (IQR)	62.5 (22.7-113.0)	34.3 (14.3-67.8)	37.6 (16.5-64.6)	62.5 (44.3-85.6)
Gleason score, n (%)				
≤6	1876 (47.2)			550 (8.0)
7	38 (1.0)	N/A	N/A	4730 (69.2)
≥8	3 (0.1)			1554 (22.7)
N/A	2061 (51.8)			60 (0.9)

IQR, interquartile range; mos, months; N/A, not available; PC, prostate cancer; SD, standard deviation.

- Across databases, correlation coefficients were strong between rwMFS and rwOS (Fleischer's *r* range: 0.988-0.999) and moderate between rwEFS and rwOS (*r* range: 0.515-0.572) and rwNED and rwOS (*r* range: 0.434-0.569) (Figure 1)
- Kendall's tau analysis revealed a positive association between the ICEs and OS

Figure 1: Correlation coefficients were strong between rwMFS and rwOS (A) and moderate between rwEFS and rwOS (B) and rwNED and rwOS (C)

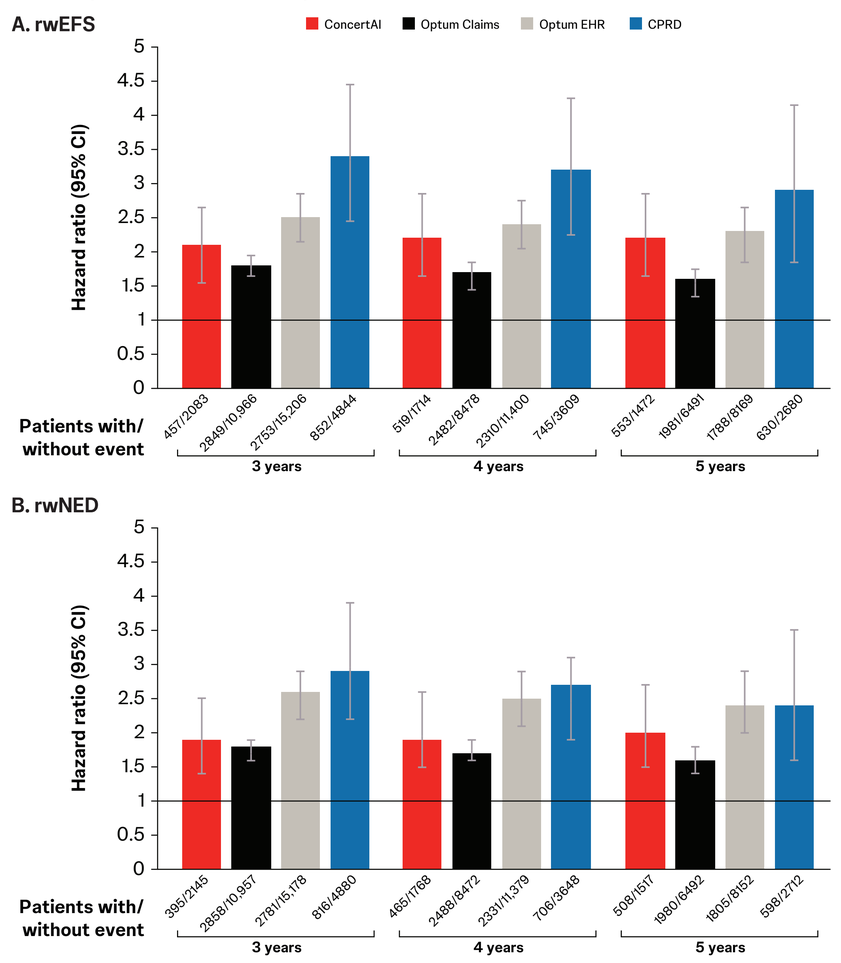


Most of the events in MFS were deaths and not metastatic events; this may explain in part the stronger correlation with OS.

Kendall's tau was higher than Fleischer's *r* for rwEFS-rwOS and rwNED-rwOS; this may reflect the methodological treatment of censored observations and the statistical assumptions underlying each measure.

- Patients without landmark rwEFS or rwNED events (non-progressors) had better rwOS than those with such events (progressors), with statistical significance (Figure 2)
  - HR ranges for rwEFS/rwNED were 3 year, 1.8-3.4/1.8-2.9; 4 year, 1.7-3.2/1.7-2.7; and 5 year, 1.6-2.9/1.6-2.4, across the 4 databases

Figure 2: Landmark analyses of rwOS according to ICE landmark-event status (rwEFS and rwNED)[a]



[a]Landmark analysis performed with EFS and NED. MFS has been validated as a surrogate endpoint for OS.[3]
95% CIs not crossing 1 indicate statistically significant differences in hazard between groups.

- In the Optum Claims, Optum EHR, and CPRD databases, there was a trend of decreasing HRs from the 3-year landmark to the 5-year landmark
- One explanation for this trend is that patient cohorts evaluated at the 3- and 5-year landmarks represent distinct populations due to survival-based selection
  - The 5-year landmark population consists of longer-term survivors who may possess more favorable prognostic characteristics compared with the 3-year landmark population, which includes patients who will experience events between years 3 and 5
- HRs derived from the claims database were consistently lower than those observed in the other databases that utilize EHR data or combined EHR/claims data. The lower HRs in Optum Claims data suggest that while the relationship direction and strength remain consistent, the magnitude of effect may vary by data source
  - One potential explanation for this is the inherent delay in claims processing. Patients may experience longer time to diagnosis documentation or administrative delays in claims submission, potentially attenuating the observed associations
  - In contrast, EHR-based databases likely capture clinical events more contemporaneously, providing a more temporally accurate representation of the patient journey at different landmark timepoints

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Prostate Cancer

Presented by B Jahn at ISPOR Europe 2025; November 9-12, 2025; Glasgow, Scotland, UK