Real-World Survival Outcomes in Medicare Patients with Intermediate-to-High-Risk Non-Muscle Invasive Bladder Cancer: Estimating Event-Free Survival and Evaluating Its Prediction to Overall Survival

Anthony Eccleston,[1] Jane Chang,[2] Julia Brinkmann,[3] Joseph C. Cappelleri,[2] Leo Chen,[2] Jordan Banks,[4] Amy Schroeder,[4] Mandar Karhade,[4] Mariia Salova,[4] Alexis Garduno[4]

[1]Pfizer, Surrey, UK; [2]Pfizer, NYC, USA; [3]Pfizer, Berlin, Germany; [4]Avalere Health, Washington, D.C., USA

Objective

To determine whether estimated event-free survival (EFS) is a predictor for overall survival (OS) in patients with Intermediate-to-High-Risk Non-Muscle Invasive Bladder Cancer (IRHR-NMIBC) who receive adequate Bacillus Calmette-Guerin (BCG) maintenance therapy (defined as ≥7 installations of BCG within 274 days of BCG initiation).

Conclusions

Results using Medicare data suggest that EFS is a strong predictor of OS in adequately treated IRHR-NMIBC patients. We recommend that EFS should be further investigated as a surrogate endpoint of OS for clinical trials and for clinical practice.

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Presenting author: Anthony Eccleston

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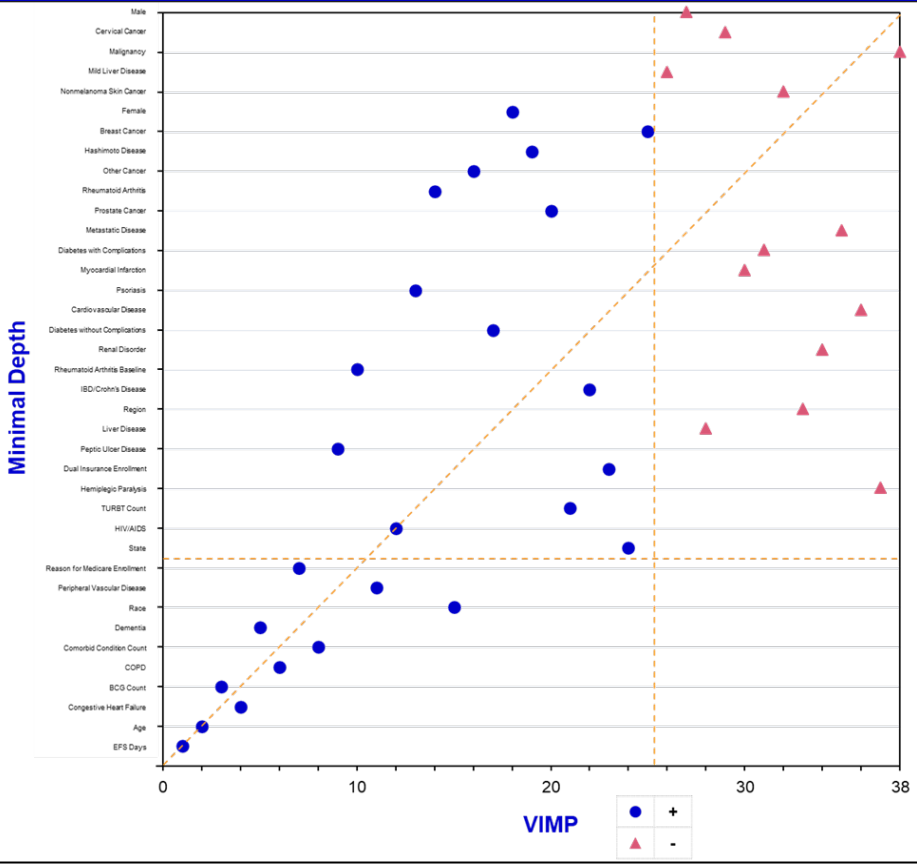Presented at ISPOR • May 5–8, 2024 • Atlanta, GA

Background or Introduction

- Bladder cancer (BC) is the sixth most common cancer in the US, with an estimated 82,290 new cases in 2023.[1] BC frequently occurs in older individuals, with an average age at diagnosis of 73 years and a 5-year relative survival rate of 77%.[2]
- Approximately 75% of patients with BC are diagnosed with NMIBC.[3] Among NMIBC patients, the 5-year probability of progression in the intermediate- to very-high risk groups ranges from 4.9% (confidence interval [CI]: 3.4%-7.0%) to 40% (CI: 29%-54%), respectively.[4]
- Treatment guidelines for NMIBC include risk stratification to guide treatment decision making.[5-9] Standard of care for IRHR-NMIBC includes transurethral resection (TURBT) followed by BCG induction and 1–3 years of BCG maintenance.[5-7,9]
- EFS has been listed in the FDA Table of Surrogate Endpoints to be used for accelerated or traditional approval of drug efficacy in oncology.[10]
- This poster supports the suitability of EFS as a surrogate endpoint for OS in NMIBC.

Materials and Methods

- **Study Population:** Patients with IRHR-NMIBC who received adequate BCG maintenance therapy (defined as ≥7 installations of BCG within 274 days of BCG initiation).[11]
- **Study Design:** Non-interventional, retrospective cohort study using the complete sample (100%) of Medicare Fee-for-Service (FFS) beneficiaries with IRHR-NMIBC.
- **Predictor of Interest:** Estimated EFS was defined as the time in days from the index date (date of BCG initiation; inclusive) to the first occurrence of an event indicating disease progression, recurrence, or death, during the follow-up period. EFS was estimated using ICD and CPT codes indicative of recurrence of high-grade disease – subsequent procedures/treatments, progression to metastatic disease, and persistence of carcinoma in situ as proxies for disease progression/recurrence.
- **Outcome:** OS was measured as the time in days from the index date to the validated date of death from any cause.
- **Random Survival Forest (RSF),** a supervised machine learning approach, was developed to elucidate variable importance for prediction of OS.
  - Using sociodemographic and clinical characteristics of patients, 1,000 "trees" were grown using sampling without replacement, and nodes were split using log-rank criteria. The RSF was trained on a 70% random sample and tested on 30% of the dataset.
  - The variable importance (VIMP) and minimal depth criteria were used to identify the most important variables in predicting OS.
  - Variables selected based on VIMP and other criteria were used to conduct a survival tree analysis that provided thresholds to classify only relevant variables.
- **Model Evaluation:** Classified age and EFS were subsequently used in a time-dependent Cox regression to predict OS; violation of the proportional hazard's assumption in the original Cox regression model allowed for identification of these time-varying effects in the time-dependent Cox model.
  - A second multivariable Cox regression model investigated the strength of continuous, quarterly EFS as a predictor of OS for comparison to the first Cox model.
- For robustness, RSF was rerun excluding patients with death as a first event and relevant predictors. The same restriction was repeated for the Cox model using both RSF-classified and continuous EFS.

Results

- 19,859 patients with IRHR-NMIBC and adequate BCG were identified from 2010-2020.
- The median follow-up period for OS was 46.3 months. During the follow-up period, 10,008 patients had ≥1 event and 5,573 deaths were captured. The median EFS time was 31.5 months (CI 95%: 31.0, 31.9). The Harrell's C-Index for both train and test sets were 0.809 and 0.813, respectively.
- The EFS time and age were identified as the most predictive covariates of OS based on the RSF model (Figure 1).
- Using the strongest predictors from the earlier RSF model, the survival tree cox model identified EFS as the first node and therefore the strongest predictor of OS. This survival tree cox model also binarized EFS at 41.5 months and created binary age splits dependent on total EFS (78 years, and 80 years; Figure 2).
- Cox regression results showed longer EFS, measured in 3-month periods, was associated with longer OS (HR: 0.96 p < 0.01, model concordance 0.67).
- Cox regression based on the survival tree (binary EFS, reference < 41.5 months) showed longer EFS was associated with longer OS (HR: 0.05, p<0.01, model concordance 0.65; Tables 1, 2). Observations were captured quarterly to account for time-varying effect.
- After excluding individuals with death as a first event (n=36), we observed similar results compared to the primary models.

Figure 1. Variable Predictive Power for OS Using Variable Importance and Minimal Depth in Tree Plot
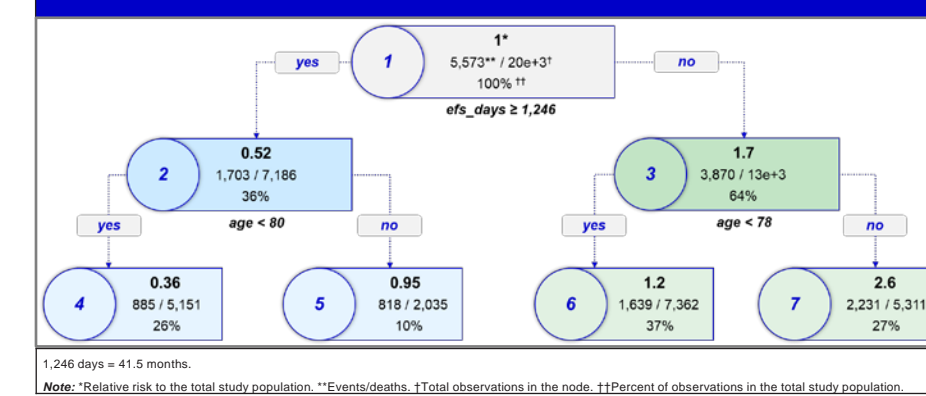

Abbreviations: AIDS – Acquired Immunodeficiency Syndrome; BCG – Bacillus Calmette-Guerin; COPD – Chronic Obstructive Pulmonary Disease; EFS – Event-Free Survival; HIV – Human Immunodeficiency Virus; IBD – Inflammatory Bowel Disease; TURBT – Transurethral Resection of Bladder Tumor.

Note: The first ten covariates (EFS Days, Age, Congestive Heart Failure, BCG Count, COPD, Comorbid Condition Count, Dementia, Race, Peripheral Vascular Disease, Reason for Medicare Enrollment), are the most predictive for EFS-OS correlation when using both variable importance and minimal depth criteria.

Figure 2. Survival Tree, Pruned; EFS Days and Age

1,246 days = 41.5 months.

Note: *Relative risk to the total study population. **Events/deaths. †Total observations in the node. ††Percent of observations in the total study population.

Table 1. Cox Regression Model Using Continuous Age and Survival-Tree Classified Binary EFS

n = 1,063,379; number of events = 5,742

	HR	SE	Robust SE	P-value	CI (95%)	
EFS Binary*	0.603	0.039	0.040	<0.001	0.558	0.652
Age, years	1.076	0.002	0.002	<0.001	1.072	1.081
Concordance†	0.651 (SE = 0.004)					
Logrank test	P<0.001					

Abbreviations: CI – Confidence Interval; EFS – Event-Free Survival; HR – Hazard Ratio; SE – Standard Error.

Note: *EFS Binary: The reference group is less than 41.5 months, and the non-reference group is greater than or equal to 41.5 months. † Concordance indicates model fit and the probability of agreement of any two randomly chosen observations, where shorter survival time correlates with a larger risk score (maximum score or perfect agreement=1).

Table 2. Cox Regression Model Using Continuous Age and Quarterly EFS

n = 361,103; number of events = 5,628

	HR	SE	Robust SE	P-value	CI (95%)	
EFS, 3 months	0.963	0.002	0.002	<0.001	0.959	0.967
Age, years	1.076	0.002	0.002	<0.001	1.072	1.080
Concordance†	0.665 (SE = 0.004)					
Logrank test	P<0.001					

Abbreviations: CI – Confidence Interval; EFS – Event-Free Survival; HR – Hazard Ratio; SE – Standard Error.

Limitations and Further Work

- Coding limitations to identify NMIBC and risk groups required the use of a validated, clinical definition from the literature to determine IRHR-NMIBC groups.
- Due to the world supply shortages of BCG and other issues including tolerance, not all patients who qualify for adequate BCG maintenance therapy receive it.
- Classification of EFS should be repeated in other cohorts to confirm reproducibility of this classification using a single survival tree, which may be prone to some instability or overfitting.[13]
- Administrative claims data do not include such information as cancer staging, laboratory test results, and other prognostic data.[14] Other morbidities considered in the RSF may be subject to misclassification, because the primary use of this data is for reimbursement purposes.
- The findings of this study are generalizable to broader FFS or Medicare Advantage populations, and so conversely, are not nationally representative for those younger than 65 years old.[12]