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Post distant recurrence survival of muscle-invasive urothelial carcinoma patients with prior radical cystectomy: analysis of a Flatiron real-world cohort matched to CheckMate 274

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Introduction

- Urothelial carcinoma (UC) develops with the growth of abnormal tissues in the urothelial cells lining the mucosal surfaces of the lower urinary tract (including the urethra and bladder) and upper urinary tract (including the renal pelvis and ureters)
- UC is the most common form of bladder cancer worldwide. Among all UC cases, 25% are classified as muscle-invasive (MIUC) and 11% are locally advanced or metastatic (aUC)[1]
- When bladder cancer invades the muscle of the bladder wall, it is associated with a high risk of mortality, unless treated with either radical cystectomy (RC) or radical radiotherapy
- Although RC has a curative intent, patients often relapse after undergoing RC, with the possibility of cancer returning to the bladder, and spreading to the lymph nodes and/or other parts of the body such as the lungs, liver, or bones[2]
- CheckMate 274 is a phase 3, multicenter, double-blind, randomized controlled trial investigating adjuvant nivolumab versus placebo in patients with high-risk MIUC who have had radical surgery within 120 days before randomization, with or without prior neoadjuvant cisplatin-based chemotherapy[3]
  - Due to lack of mature overall survival (OS) data from the trial, post-distant recurrence (DR) survival data was is limited in CheckMate 274
- Despite up to 50% of patients with MIUC developing advanced urothelial carcinoma (aUC) by experiencing DR after undergoing RC in the real world,[4] there is limited research in the published literature investigating survival trend of this population after DR and related long-term projection

Objective

- To describe the post DR survival (PDRS) outcomes of aUC patients with a history of RC in a real-world cohort matched to the characteristics of a subgroup of CheckMate 274 population who experienced DR

Methods

Definition of the real-world patient cohort

- The Flatiron Health cancer database is a longitudinal real-world database in the United States comprising de-identified, patient-level structured and unstructured data, curated via abstraction of electronic health records[5]
- The cohort of patients from Flatiron was refined according to the following criteria:
  - Inclusion criteria:
    - Adults with an aUC diagnosis between January 1, 2011, and February 18, 2022
    - Had undergone a complete radical cystectomy
    - Had at least 1 month of medical data after the initial aUC diagnosis
    - No restrictions on therapies received for aUC treatment
  - Exclusion criteria:
    - Had no surgery; or surgery other than complete RC
    - Had a complete RC at or after the aUC diagnosis

Propensity score matching

- Matching was performed by forming pairs between patients in Flatiron health database and the CheckMate 274 trial according to their propensity scores (PS), which were estimated via logistic regression. The MatchIt package in R was used for the PS matching, and the analysis followed the steps proposed by Zhao et al[6]
- After the calculation of PS, the nearest-neighbor matching algorithm was applied without replacement and a caliper width of 0.2[6,7]
- The initial model included all candidate variables initially selected for matching and available in the database (age at aUC diagnosis, sex, Eastern Cooperative Oncology Group performance status [ECOG PS], and race). Analyses included only patients with a record for each matching variable of interest
- A sequential approach was performed to remove the least important matching variables to try to achieve a balanced matched cohort. Covariates with a standardized mean difference (SMD) > 0.1 were considered as out of balance
- For each model run in the sequential approach, the sample size of the matched population and the quality of matches were subsequently assessed by investigating the covariate balance after matching, using both graphical and statistical methods, and comparing the size of the matched cohort with the original sample size

Survival analysis

- The cohort-specific PDRS was estimated once the matched cohort was identified
- Time-to-event analyses were undertaken to estimate PDRS from the time of aUC diagnosis until death by any cause using standard Kaplan-Meier methodology[8]
  - Patients who were lost to follow-up or alive at the last point of contact (i.e., by the last observed medical visit, procedure, or medication administration date as entered in the Flatiron database) were censored
- Match-adjusted survival of the real-world cohort was extrapolated using 7 standard parametric and 6 spline models as recommended by National Institute for Health and Care Excellence DSU TSD 14[9]

Results

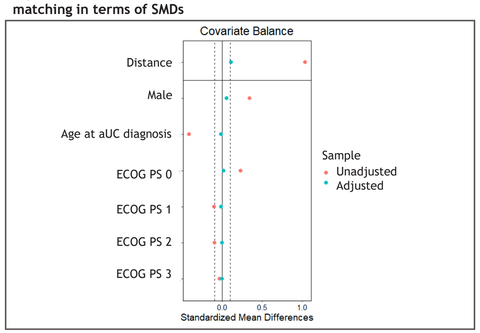
Cohort disposition

- Of the 10,912 patients with aUC identified from the Flatiron Health database, 461 met the study inclusion criteria for the final analysis cohort
  - Although patients with upper tract urothelial carcinoma were included, a majority were bladder cancer patients
- Of the 709 patients studied in the CheckMate 274 trial, 259 had a DR at time of data analysis (database lock, February 2021) and were included in the analysis

Matched cohort characteristics

- The initial model that included all candidate variables was not balanced (SMDs > 0.1) and produced a matched cohort that was reduced to 52% (n = 134) of the original sample size of the DR population in CheckMate 274
- Both race and ECOG PS had a high degree of missing data. Following the sequential approach, race was deemed clinically less important than ECOG PS and removed from consideration as a matching variable
- Matching based on sex, age at aUC, and ECOG PS resulted in balanced covariate distributions between cohorts (SMDs < 0.1 for all covariates) with the final matched cohort reduced to 71% (n = 184) of the original sample size of the DR population from CheckMate 274 (**Table 1** and **Figure 1**)
- In the matched real-world cohort, the mean age at aUC diagnosis was 68 years, and 63% of the cohort was male. Half of the matched cohort had an ECOG PS of 0, 44% had an ECOG PS of 1, and the remaining 4% had an ECOG PS of 2
- Additional baseline characteristics of the matched real-world cohort cohort are presented in **Table 2**

Figure 1. Visual summary of the covariate balance before and after matching in terms of SMDs



Dashed lines indicate the threshold of 0.1 SMD which was used to evaluate covariate balance. The distance measure indicates the propensity score difference.
ECOG PS 0/1/2/3: Proportion of patients with ECOG PS 0/1/2/3, Male: Proportion of male patients

Survival analysis for the matched cohort

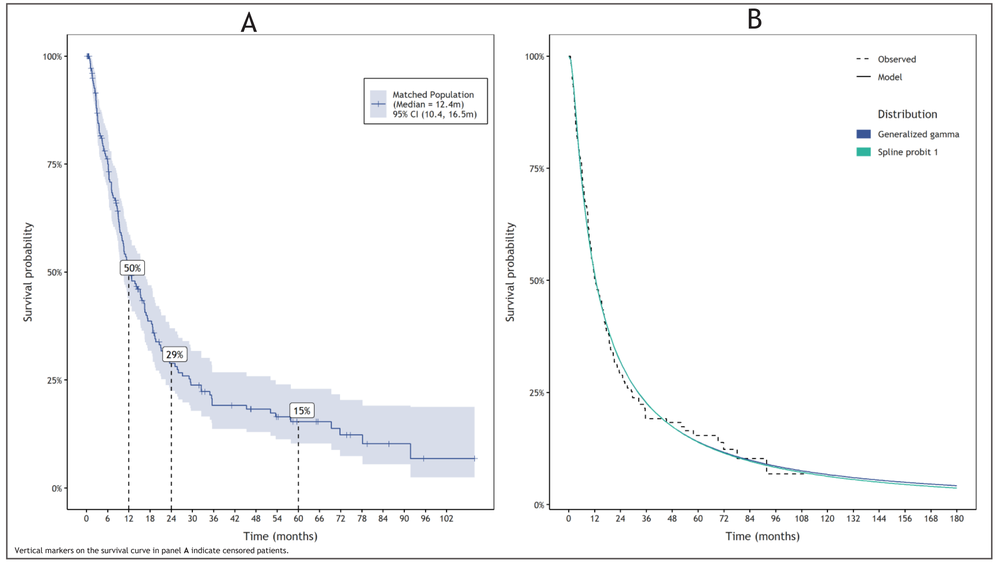
- Median follow-up in this population was 57.6 (95% confidence interval [CI], 46.7-74.7) months
- The Kaplan-Meier curve for the observed PDRS of the matched cohort is presented in the left-hand panel of **Figure 2**
- The median PDRS among the matched cohort was estimated to be 12.4 months. Estimated 1-, 2- and 5-year PDRS rates (95% CI) 50% (43–59), 29% (23-37), and 15% (10–23), respectively
- Based on Akaike information criterion–and visual comparison of the candidate model fits to the observed data, generalized gamma and spline probit 1-knot models were the best performing models (**Figure 2**).

Table 1. Covariate distribution in the unmatched and matched cohorts

Covariate	Before matching			After matching		
	Flatiron (N = 347)[a]	CheckMate 274 (N = 259)	SMD	Flatiron (N = 184)	CheckMate 274 (N = 184)	SMD
Sex, n (%)						
Female	201 (57.9)	61 (23.6)		69 (37.5)	59 (32.1)	
Male	146 (42.1)	198 (76.4)	−0.34	115 (62.5)	125 (67.9)	0.05
Mean (SD) age at aUC diagnosis, years	71 (8.6)	67 (9.6)	−0.41	68 (9.0)	68 (8.6)	−0.01
ECOG PS, n (%)						
0	129 (37.2)	156 (60.2)	0.23	96 (52.2)	99 (53.8)	0.02
1	164 (47.3)	96 (37.1)	−0.10	81 (44.0)	78 (42.4)	−0.02
2	42 (12.1)	7 (2.7)	−0.09	7 (3.8)	7 (3.8)	0.00
3	12 (3.5)	0	−0.03	0	0	0.00

[a]Of the 461 patients meeting the inclusion criteria, only 347 had information for all matching criteria.
SD, standard deviation.

Figure 2. PDRS curve (panel A) and best fitting survival models for the matched Flatiron cohort (panel B)



Vertical markers on the survival curve in panel A indicate censored patients.

- Restricted mean survival time (RMST) at 84-months, calculated as area under the survival curve, was 24.1 months for the matched population.
- For the matched population, estimated RMST at year 15 was 30.1 and 29.6 months for the generalized-gamma and spline probit 1 models, respectively.

Discussion

- This study generated a matched cohort of patients from the Flatiron database with similar characteristics to those with DR who participated in the CheckMate 274 trial via a PS matching approach, and described the survival observed after DR
- The analysis of PDRS of this real-world cohort confirmed that patients who experienced DR can still have poor survival outcomes in the real-world despite having undergone a prior RC. The results from these analyses are in line with previously published estimates by Geynisman et al[1]; however, it must be noted that the study population in Geynisman et al was not limited to aUC patients who had undergone a complete RC before DR
- A key limitation of this study is missing data on clinically important covariates that were not assessed at or before DR (eg, initial tumor origin, pathological tumor stage, nodal status, and neoadjuvant treatment status before RC). Small sample sizes of the cohorts and their missing data on estimated glomerular filtration rate [eGFR] limited subgroup analyses by cisplatin eligibility

Table 2. Additional baseline characteristics in the matched Flatiron cohort

Covariate	Flatiron cohort (N = 184)
Race, n (%)	
White	134 (72.8)
Black or African American	10 (5.4)
Other	27 (14.7)
Unknown	13 (7.1)
Ethnicity, n (%)	
Hispanic or Latino	12 (6.5)
Not Hispanic or Latino	147 (79.9)
Not reported	25 (13.6)
Disease site at diagnosis, n (%)	
Bladder	179 (97.3)
Renal pelvis	1 (0.5)
Ureter	4 (2.2)
Mean (SD) time from RC to DR, years	2 (2.5)
Smoking status, n (%)	
Current/former smoker	133 (72.3)
Never smoked	46 (25.0)
Unknown	5 (2.7)
Cisplatin eligibility,[a] n (%)	
Eligible	44 (23.9)
Ineligible	33 (17.9)
Unknown	107 (58.2)
First-line treatment class, n (%)	
Best supportive care[b]	38 (20.7)
Carboplatin-based[c]	52 (28.3)
Cisplatin-based[d]	26 (14.1)
Immunotherapy[e]	43 (23.4)
Other chemotherapy[f]	16 (8.7)
Other[g]	9 (4.9)

[a]Patients who had an eGFR ≥ 60 mL/min and ECOG PS < 2 or missing were classified as eligible, patients with eGFR < 60 mL/min or ECOG ≥ 2 were classified as ineligible, whereas patients with no record of eGFR and ECOG were classified as unknown. [b]Patients who did not receive any defined systemic treatment known for treating UC, or any treatment that was not cisplatin, carboplatin, other-chemotherapy, or an IO. [c]Patients who received carboplatin as monotherapy or in combination therapy. [d]Patients who received cisplatin as monotherapy or in combination therapy, where cisplatin took priority if a patient received cisplatin in combination with carboplatin. [e]Patients who received an IO as monotherapy or in combination therapy, where IO took priority when in combination with cisplatin or carboplatin. [f]Patients who received monotherapy or combination chemotherapy in absence of cisplatin, carboplatin, or an IO. [g]Patients who received a non-defined systemic treatment (ie, clinical study drug).
IO, immunotherapy; DR, distant recurrence; SD, standard deviation.

Conclusions

- This study provided real-world survival estimates for patients with aUC who underwent RC before DR, filling the present knowledge gap and highlighting an unmet medical need in this population
- Results demonstrated only 50% of patients survive 1 year in this setting
- PDRS outcomes for the matched cohort can be compared against the actual PDRS in CheckMate 274 once mature OS data becomes available from the trial
- Match-adjusted survival analyses by cisplatin eligibility status and first-line treatment class were subject to substantial uncertainty due to limited sample size and missing data in each category

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Acknowledgments

- This study was supported by Bristol Myers Squibb (Princeton, NJ)
- All authors contributed to and approved the presentation; analytical and writing assistance was provided Open Health, funded by Bristol Myers Squibb
- Editorial assistance was provided by Erika Young, PharmD, of Parexel, funded by Bristol Myers Squibb

Presented at ISPOR 2023; May 7-10, 2023; Boston, MA

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