# Impact of Statin Use on Oncologic Outcomes in Patients with Urothelial Carcinoma of the Bladder Treated with Radical Cystectomy

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**Purpose:** Statins are cholesterol lowering agents used to prevent cardiovascular disease. Evidence suggests a dichotomous effect of statins with cancer inhibiting and promoting properties. To our knowledge the effect of statins on the prognosis of muscle invasive urothelial carcinoma of the bladder remains uninvestigated to date. We tested the hypothesis that statin use impacts oncological outcomes in patients treated with radical cystectomy for urothelial carcinoma of the bladder.

**Materials and Methods:** We retrospectively evaluated the records of 1,502 patients treated with radical cystectomy and pelvic lymphadenectomy without neoadjuvant therapy at a total of 4 institutions. Cox regression models were used to determine the association of statins with disease recurrence and cancer specific mortality.

**Results:** A total of 642 patients (42.7%) were on statins. At a median followup of 34 months 509 patients (33.9%) experienced disease recurrence and 402 (26.8%) had died of urothelial carcinoma of the bladder. Statin users were older ($p = 0.003$), had a higher body mass index (median 32 vs 28 kg/m$^2$, $p < 0.001$) and were more likely to have positive soft tissue surgical margins (9% vs 4%, $p < 0.001$). On univariable Cox regression analysis statins, female gender, advanced age, higher body mass index, smoking status, tumor stage, tumor grade, soft tissue surgical margin status, lymphovascular invasion, lymph node metastasis and adjuvant chemotherapy were associated with disease recurrence ($p \leq 0.05$) and cancer specific mortality ($p \leq 0.02$). On multivariable Cox regression analysis statin use was not associated with either outcome.

**Conclusions:** Statin users were at higher risk for disease recurrence and cancer specific mortality on univariable but not multivariable analysis. These data do not support modification of statin use in patients with high risk urothelial carcinoma of the bladder who will be treated with radical cystectomy.

**Key Words:** urinary bladder, urinary bladder neoplasms, neoplasm recurrence, mortality, hydroxymethylglutaryl-CoA reductase inhibitors

**Abbreviations and Acronyms**

BMI = body mass index

CIS = carcinoma in situ

LVI = lymphovascular invasion

RC = radical cystectomy

STSM = positive soft tissue surgical margin

UCB = urothelial carcinoma of bladder

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**For another article on a related topic see page 731.**

Urothelial carcinoma of the bladder is a highly aggressive disease and a significant cause of morbidity and mortality.[1,2] RC with bilateral pelvic lymphadenectomy is the standard of care for muscle invasive and high

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risk, nonmuscle invasive UCB. Statins, a class of drug commonly used to control cholesterol, have demonstrated cardiovascular benefits resulting in decreases in cholesterol and venous thromboembolism.[3]

Preclinical studies suggest that statins have a paradoxical immunomodulatory property in that they inhibit tumor cell proliferation and induce apoptosis or increase growth potential.[4–7] For nonmuscle invasive UCB most studies showed no association between statin use and disease recurrence or progression in patients treated with intravesical bacillus Calmette-Guérin.[8,9] For advanced UCB only 1 retrospective, single institution study to date has evaluated the impact of statins on local control in patients treated with a combination of chemotherapy and radiotherapy.[10] In that series statin use resulted in better local disease control.

To our knowledge no group to date has evaluated the association of statin use with outcomes in patients treated with RC. Therefore, we assessed the impact of statins on oncological outcomes in patients treated with RC for UCB. Based on the previous study of muscle invasive UCB,[10] we hypothesized that statins would be associated with lower rates of disease recurrence and cancer specific mortality.

## METHODS

### Patient Selection and Data Collection

The institutional review board approved this study and all participating sites providing the necessary data sharing agreements before study initiation. From 1992 to 2008 at 4 institutions a total of 1,502 patients underwent RC and pelvic lymphadenectomy for muscle invasive UCB. Those who received preoperative chemotherapy or radiotherapy, or were diagnosed with metastatic disease were excluded from analysis. Adjuvant chemotherapy was administered in 321 patients at clinician discretion based on pathological features, and patient general health and preference. We retrospectively reviewed the patient records at each institution to confirm the status of statin use at RC.

**Table 1.** *Clinicopathological characteristics of patients treated with RC for UCB*

| | Overall | | No Statin | | Statin | | p Value |
|---|---|---|---|---|---|---|---|
| No. pts (%) | 1,502 | | 860 | (57.2) | 642 | (42.8) | — |
| No. male (%) | 1,177 | (78.4) | 682 | (79.3) | 495 | (77.2) | |
| No. female (%) | 325 | (21.6) | 178 | (20.7) | 147 | (22.8) | 0.31 |
| Mean ± SD age/median (IQR) | 65.5 ± 9.8/66.0 | (59–73) | 64.9 ± 10.5/66 | (59–72) | 66.3 ± 8.9/67 | (60–73) | 0.003 |
| Mean ± SD kg/m$^2$ BMI/median (IQR) | 29.67 ± 4.9/30.0 | (26–33) | 28.4 ± 5.0/28 | (24–32) | 31.2 ± 4.4/32 | (28–34) | <0.001 |
| No. smoking status (%): | | | | | | | |
| Never | 293 | (19.5) | 167 | (19.4) | 126 | (19.7) | |
| Former | 693 | (46.1) | 410 | (47.7) | 283 | (44.0) | 0.32 |
| Current | 516 | (34.4) | 283 | (32.9) | 233 | (36.3) | |
| No. pathological stage (%): | | | | | | | |
| pT0 | 77 | (5.1) | 44 | (5.1) | 33 | (5.1) | |
| pTis | 62 | (4.1) | 33 | (3.8) | 29 | (4.5) | |
| pTa | 167 | (11.1) | 90 | (10.5) | 77 | (12.0) | |
| pT1 | 170 | (11.3) | 99 | (11.5) | 71 | (11.0) | 0.36 |
| pT2 | 399 | (26.6) | 249 | (29.0) | 150 | (23.4) | |
| pT3 | 459 | (30.6) | 255 | (29.6) | 204 | (31.8) | |
| pT4 | 168 | (11.2) | 90 | (10.5) | 78 | (12.2) | |
| No. pathological grade (%): | | | | | | | |
| No tumor | 77 | (5.1) | 44 | (5.1) | 33 | (5.1) | |
| Low | 28 | (1.9) | 14 | (1.7) | 14 | (2.2) | 0.73 |
| High | 1,397 | (93.0) | 802 | (93.2) | 595 | (92.7) | |
| No. soft tissue surgical margin (%): | | | | | | | |
| Neg | 1,408 | (93.7) | 825 | (96.0) | 583 | (90.8) | <0.001 |
| Pos | 94 | (6.3) | 35 | (4.0) | 59 | (9.2) | |
| No. LVI (%): | | | | | | | |
| Absent | 1,039 | (69.2) | 592 | (68.8) | 447 | (69.6) | 0.39 |
| Present | 463 | (30.8) | 268 | (31.2) | 195 | (30.4) | |
| No. concomitant CIS (%): | | | | | | | |
| Absent | 849 | (56.5) | 497 | (57.7) | 352 | (54.8) | 0.13 |
| Present | 653 | (43.5) | 363 | (42.3) | 290 | (45.2) | |
| No. lymph node status (%): | | | | | | | |
| Negative | 1,171 | (78.0) | 673 | (78.2) | 498 | (77.6) | 0.99 |
| Positive | 331 | (22.0) | 187 | (21.8) | 144 | (22.4) | |
| Mean ± SD No. lymph nodes removed/median (IQR) | 19.2 ± 13.1/16.0 | (11–25) | 20.3 ± 5.0/17 | (24–32) | 17.9 ± 11.7/15 | (11–23) | 0.45 |
| No. adjuvant chemotherapy (%): | | | | | | | |
| No | 1,181 | (78.6) | 671 | (78.1) | 510 | (79.4) | |
| Yes | 321 | (21.4) | 189 | (21.9) | 132 | (20.6) | 0.27 |