The Association of Aspirin Use with Survival Following Radical Cystectomy

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Purpose: Aspirin may have antineoplastic properties through the inhibition of inflammatory cytokines that regulate cell proliferation, angiogenesis and apoptosis. In patients with nonmuscle invasive bladder cancer aspirin use has been linked to a reduced risk of recurrence. We evaluated the association of aspirin with survival following radical cystectomy.

Materials and Methods: A total of 1,061 patients underwent radical cystectomy at our institution between 2007 and 2016, of whom 461 (43%) were aspirin users at the time of surgery. Survival estimates were assessed by the Kaplan-Meier method. The Cox proportional hazards model was applied to evaluate associations between patient features and survival.

Results: Median followup after radical cystectomy among survivors was 4.2 years (IQR 2–6.2). During this time 442 patients died, including 331 of bladder cancer. Aspirin users were significantly older, more likely to have a history of cardiovascular disease and diabetes, and more likely to use metformin or statin (each $p < 0.05$). Nevertheless, we found that patients who ingested a daily aspirin had significantly higher 5-year cancer specific survival (68% vs 60%, $p = 0.02$) and overall survival (59% vs 52%, $p = 0.03$) compared to nonusers. Moreover, after multivariable adjustment aspirin use remained independently associated with lower cancer specific mortality (HR 0.64, 95% CI 0.45–0.89, $p = 0.01$) as well as all cause mortality (HR 0.70, 95% CI 0.53–0.93, $p = 0.02$) but not with distant metastasis ($p > 0.05$).

Conclusions: Daily aspirin use was associated with significantly improved survival outcomes following radical cystectomy. Further research is warranted to evaluate the potential underlying biological mechanisms and investigate causality.

Key Words: bladder neoplasms, cystectomy, aspirin, mortality, cytokines

Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin
COX = cyclooxygenase
CSS = cancer specific survival
MFS = metastasis-free survival
NMIBC = nonmuscle invasive bladder cancer
OS = overall survival
PGE = prostaglandin E
RC = radical cystectomy

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Aspirin may have antineoplastic properties through the down-regulation of inflammatory cytokines, leading to decreased cell proliferation, reduced angiogenesis and apoptosis promotion.[1] Indeed, an association between daily aspirin use and reduced cancer specific mortality has been demonstrated for colorectal, prostate and breast cancers.[2–4] In light of these data the USPSTF (United States Preventive Services Task Force) currently recommends initiating low dose daily aspirin in adults 50 to 59 years old with cardiovascular risk factors for the primary prevention of not only

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cardiovascular disease but also colorectal cancer.[5] However, the association between aspirin and outcomes in patients with bladder cancer remains to be defined.

Preclinical data suggest that aspirin as an irreversible COX inhibitor may have activity against urothelial cancer. Studies in rat urothelial cancer models have shown up-regulation of the COX-2 isoform in tumor tissue with an associated increase in the production of PGE2, which is thought to be procarcinogenic.[1,6] Moreover, among patients with high risk NMIBC treated with intravesical BCG aspirin use has been linked to a reduced risk of recurrence.[7,8] Nevertheless, the importance of aspirin in patients with bladder cancer who undergo RC has not been established.

Therefore, we evaluated the association between daily aspirin use and survival in patients who underwent RC.

METHODS

Study Population

After institutional review board approval we queried the cystectomy registry at our institution to identify patients who underwent RC between 2007 and 2016. Those who underwent RC for a benign indication or a nonbladder primary malignancy were excluded from study. The supplementary table (http://jurology.com/) lists the assessed patient features. Peripheral vascular disease was defined as a history of a transient ischemic attack, a cerebrovascular accident or peripheral claudication. Positive surgical margins referred to soft tissue and urothelial margins. Pathological stage was classified according to the AJCC (American Joint Committee on Cancer) system, 7th edition.[9]

In addition to aspirin use, data on metformin and statin use were collected as these agents have been previously associated with survival in patients treated with RC.[10,11]

Exposure Ascertainment

The exposure of interest was daily preoperative aspirin use. The ACE (Advanced Cohort Explorer, Mayo Clinic Center for Clinical and Translational Science, Rochester, Minnesota), a software query tool which enables detailed searches of electronic clinical records, was used to search for the terms aspirin, ASA, statin, metformin or Glucophage® in the admission or current medications sections of all clinical notes. Identified records were then individually reviewed by a single investigator (TDL). Patients were classified as aspirin users if aspirin was listed as a daily medication within 90 days prior to RC, or a discharge summary or first postsurgical clinic note indicated that the patient should resume aspirin. Patients using aspirin on demand were considered nonusers. For purposes of analysis doses were classified as low—25, 81 or 162 mg, or high—325 or 650 mg in accordance with previously established dose definitions.[12]

Outcome Measures

The primary outcomes of interest were CSS and OS. We also assessed distant MFS and local recurrence-free survival. Survival is assessed annually in our cystectomy registry. Death is attributed to bladder cancer in patients who visited our institution for metastatic bladder cancer within 6 months of death. If a death certificate is unobtainable, cause of death is verified with the patient family or local physician. Secondary outcomes included postoperative bleeding complications and perioperative transfusion requirements. Bleeding complications were defined as hematoma or hemorrhage within 90 days of RC.

Statistical Analysis

Continuous features summarized as the median and IQR were compared by the Mann-Whitney U test. Categorical features summarized as the frequency and percent were compared by the chi-square or Fisher exact test. Survival outcomes were estimated with the Kaplan-Meier method and compared using the log rank test. Cox proportional hazards models were applied to evaluate associations between patient features and survival. Features at $p \leq 0.1$ on univariate Cox analysis were included in the multivariable models, in addition to the a priori predictors diabetes, smoking, metformin and statin use, carcinoma in situ and a positive surgical margin. Interaction terms for aspirin with statins and metformin were assessed. Kaplan-Meier subset analyses were performed in patients with pathological nonmuscle invasive disease (pT1 or less) or muscle invasive disease (pT2-4) but Cox models were not assessed due to the low event rate, which limited covariate inclusion in the models. Statistical significance was considered at 2-tailed $p < 0.05$ and analyses were performed with SAS®, version 9.4.

RESULTS

A total of 1,061 patients underwent RC during the study period, of whom 461 (43%) were on daily aspirin preoperatively. The supplementary table (http://jurology.com/) lists the clinicopathological features of the overall study cohort stratified by aspirin use. Compared to patients who were not receiving aspirin those on aspirin had a higher body mass index and they were older, more likely to have cardiovascular comorbidity, more likely to be on metformin and statins and less likely to undergo continent diversion (all $p < 0.05$). There was no significant difference in the incidence of aspirin users vs nonusers in the need for perioperative blood transfusion (49% vs 49%, $p = 0.90$) or in postoperative bleeding complications (2.6% vs 2.0%, $p = 0.51$).

Median followup among survivors was 4.2 years (IQR 2–6.4). During this time 442 patients died, including 331 of bladder cancer. We found that 5-year CSS (68%, 95% CI 63–73 vs 60%, 95% CI 56–65, $p = 0.02$) and OS (59%, 95% CI 54–64 vs 52%, 95% CI 48–57, $p = 0.03$) were significantly

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higher among aspirin users compared to nonusers. Aspirin use was not associated with 5-year local recurrence-free survival (87%, 95% CI 83–90 vs 85%, 95% CI 82–89, p = 0.69) or MFS (68%, 95% CI [F1] 64–73 vs 69%, 95% CI 65–73, p = 0.94, fig. 1). After multivariable adjustment aspirin use remained associated with a significantly decreased risk of death from bladder cancer (HR 0.64, 95% CI 0.45–0.89, p = 0.01) as well as all cause mortality [T1] (HR 0.70, 95% CI 0.53–0.93, p = 0.02, table 1).

On subset analysis of pathological stage in patients with pathological nonmuscle invasive disease aspirin use was significantly associated with improved 5-year OS (81%, 95% CI 75–87 vs 72%, 95% CI 66–78, p = 0.04) and CSS (90%, 95% CI 86–95 vs 81%, 95% CI 76–87, p = 0.02) but not with MFS (87%, 95% CI 82–92 vs 86%, 95% CI 81–92, [F2] p = 0.60, fig. 2). There was no significant difference in survival outcomes between the groups in patients [F3] with pathological T2-4 disease (fig. 3).

The daily aspirin dose was 25 mg in 2 of the 461 aspirin users (0.4%), 81 mg in 373 (81%), 162 mg in 19 (4%), 325 mg in 66 (14%) and 650 in 1 (0.2%). Patients receiving low dose aspirin had significantly higher 5-year CSS and OS but not MFS compared to patients on a high dose and those on no aspirin (supplementary figure, http://jurology.com/). There was no significant difference in CSS (p = 0.17), MFS (p = 0.11) or OS (p = 0.09) on pairwise comparison between low and high dose aspirin users (data not shown). Further, on multivariable analyses low dose aspirin vs aspirin nonuse was associated with significantly decreased cancer specific mortality (HR 0.61, 95% CI 0.46–0.81) as well as all cause mortality (HR 0.62, 95% CI 0.49–0.80, each p <0.001). No significant survival benefit was observed for high dose aspirin (p >0.05, table 2).

Due to the small number of high dose users we performed sensitivity analysis with the definition of high dose changed to include 162 mg as well as 325 and 650 mg. However, this analysis did not change any reported findings (data not shown).

DISCUSSION

In the current study we found a beneficial association between daily preoperative aspirin use and postoperative cancer specific survival as well as overall survival following RC. These associations were maintained after controlling for relevant clinicopathological prognostic features. At the same time patients on aspirin preoperatively did not have

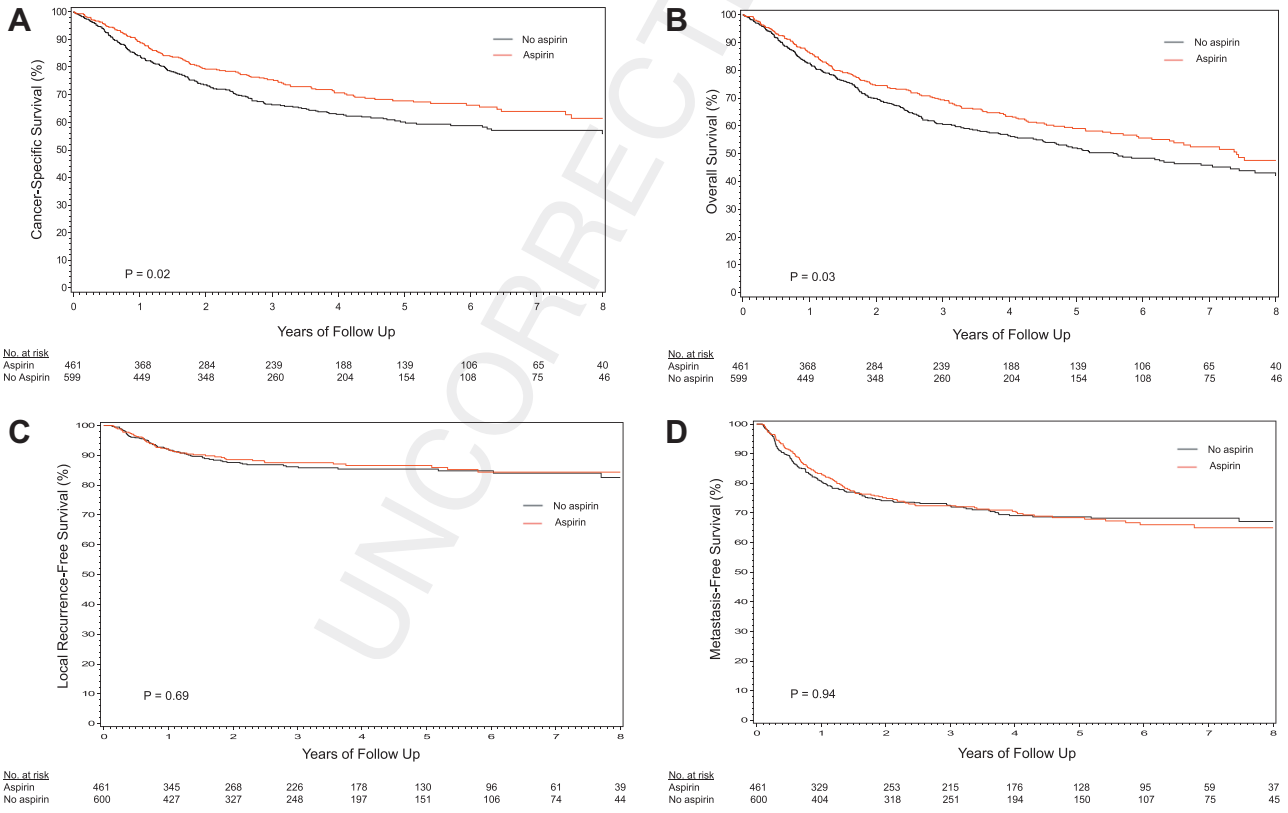

Figure 1. Kaplan-Meier curves of cancer specific (*A*), overall (*B*), local recurrence-free (*C*) and metastasis-free (*D*) survival stratified by preoperative aspirin use.

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Table 1. *Multivariable Cox proportional hazards analysis of factors associated with death after radical cystectomy*

	Distant Metastasis		Ca Specific Mortality		All Cause Mortality	
	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Age/10-yr increase	1.14 (0.97–1.33)	0.10	1.14 (0.99–1.31)	0.07	1.21 (1.06–1.37)	0.004
ECOG 0, 1, 2+	1.12 (0.86–1.46)	0.41	1.20 (0.96–1.50)	0.12	1.35 (1.12–1.62)	0.001
Body mass index	0.99 (0.97–1.02)	0.49	0.97 (0.95–0.99)	0.02	0.98 (0.96–0.99)	0.01
Use:						
Aspirin	0.96 (0.68–1.36)	0.83	0.64 (0.45–0.89)	0.01	0.70 (0.53–0.93)	0.02
Metformin	1.34 (0.64–2.78)	0.44	0.59 (0.28–1.25)	0.17	0.62 (0.33–1.15)	0.13
Statin	1.09 (0.71–1.69)	0.69	1.15 (0.78–1.68)	0.48	1.22 (0.88–1.69)	0.23
Aspirin/10-yr increase:						
Metformin	0.97 (0.41–2.33)	0.95	1.72 (0.73–4.07)	0.21	1.52 (0.73–3.18)	0.27
Statin	1.02 (0.58–1.80)	0.95	0.99 (0.59–1.69)	0.99	0.81 (0.52–1.27)	0.35
Pathological T stage:						
Less than T2	Referent	—	Referent	—	Referent	—
T2	1.98 (1.30–3.03)	0.002	1.91 (1.28–2.85)	0.002	1.48 (1.07–2.03)	0.02
T3/4	5.54 (3.97–7.75)	<0.001	5.53 (4.02–7.59)	<0.001	3.58 (2.77–4.62)	<0.001
Pathological node pos	2.55 (1.86–3.50)	<0.001	3.02 (2.26–4.04)	<0.001	2.86 (2.20–3.71)	<0.001
Periop blood transfusion	1.32 (1.002–1.75)	0.049	1.77 (1.36–2.30)	<0.001	1.79 (1.43–2.25)	<0.001

Adjusted for gender, history of coronary artery disease/myocardial infarction, peripheral vascular disease, congestive heart failure, diabetes, smoking, neoadjuvant chemotherapy, adjuvant chemotherapy, diversion type, pathological carcinoma in situ, total number of lymph nodes removed, positive surgical margin and estimated blood loss.

an increased rate of perioperative blood transfusion or bleeding complications. Subset analyses suggested that a beneficial association with aspirin may be limited to patients with pathologically nonmuscle invasive disease and patients on low dose aspirin.

The observed effect size of aspirin use with cancer specific mortality (HR 0.64) is similar to that documented for other malignancies. A meta-analysis of available studies on aspirin use and cancer showed a cause specific HR of 0.71, 0.69 and 0.94 favoring

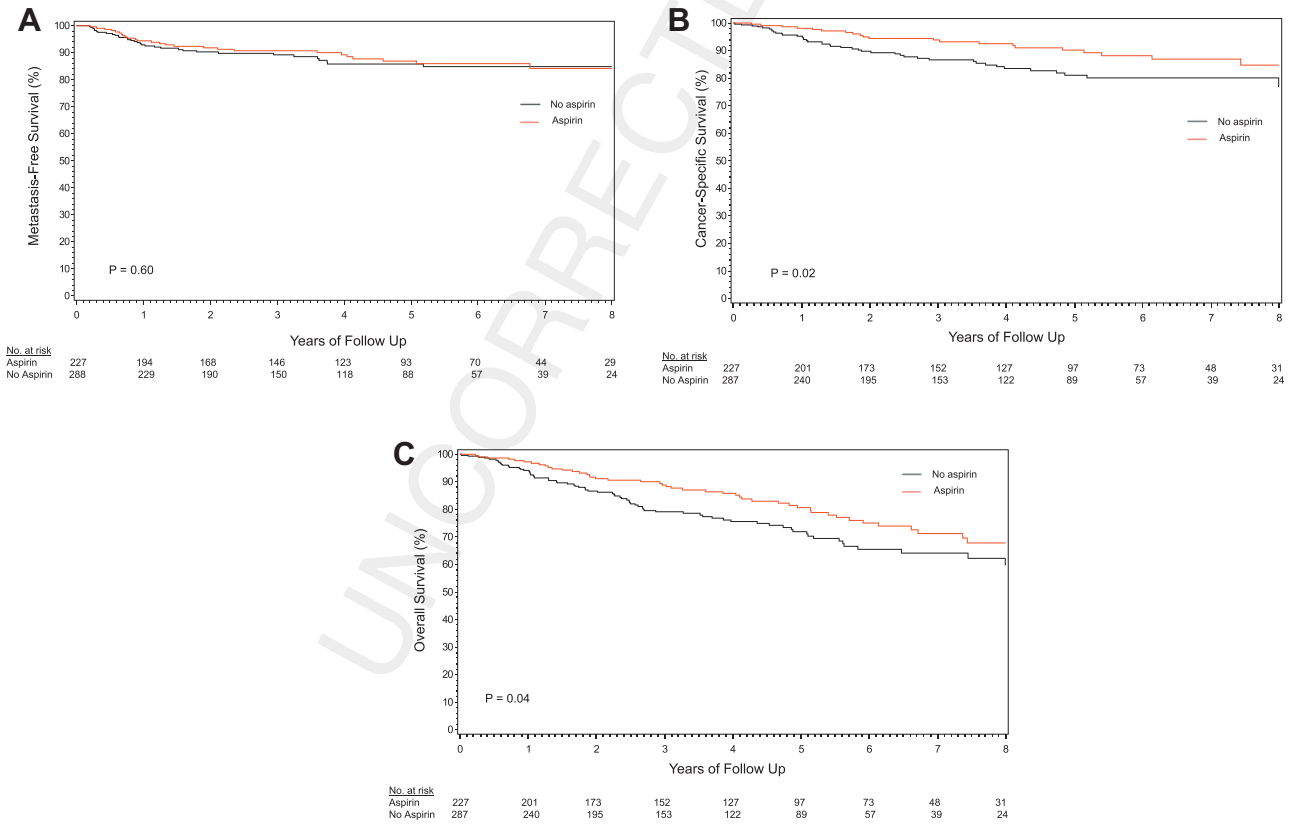

Figure 2. Kaplan-Meier curves of metastasis-free (*A*), cancer specific (*B*) and overall (*C*) survival in patient subset with pathological nonmuscle invasive disease.

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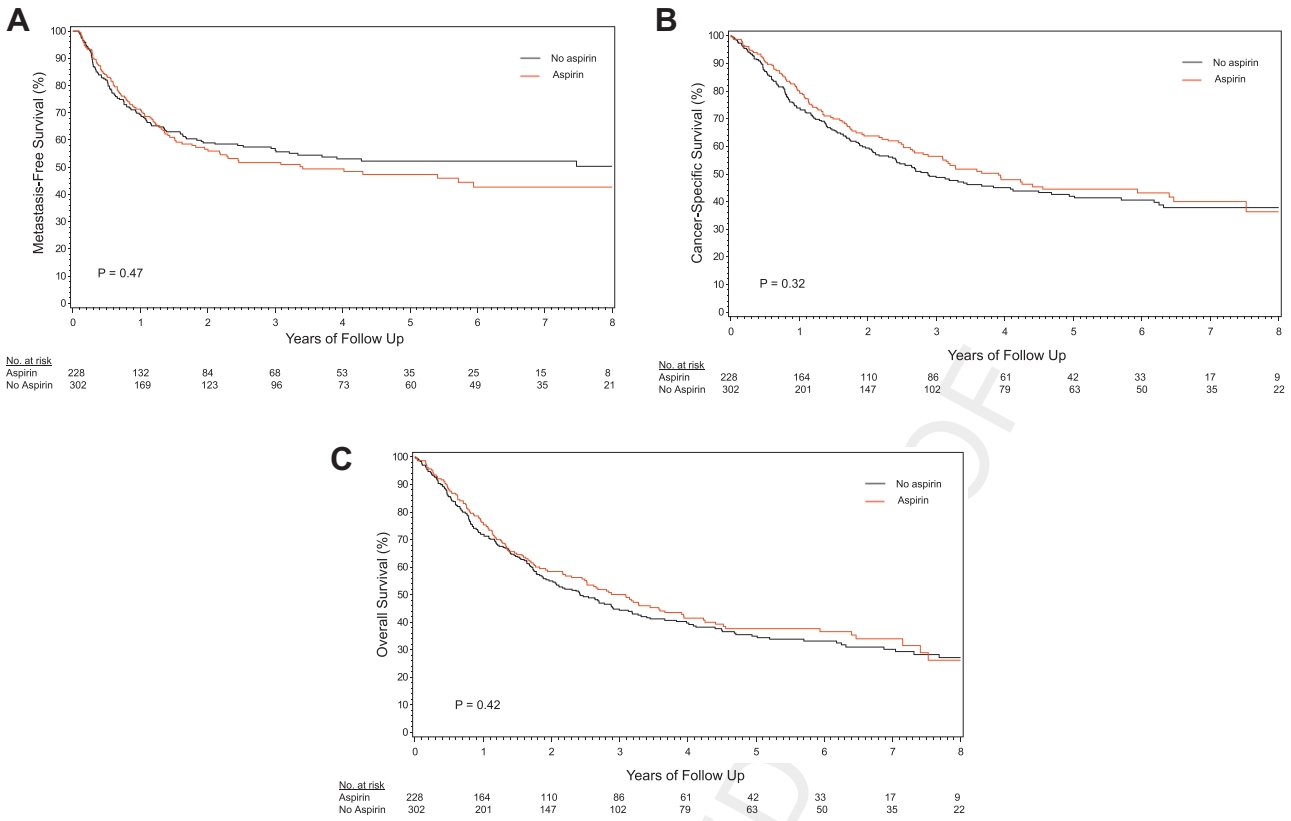

Figure 3. Kaplan-Meier curves of metastasis-free (*A*), cancer specific (*B*) and overall (*C*) survival in patient subset with pathological T2-4 disease.

aspirin users with colorectal, breast and prostate cancers, respectively.[2] Moreover, preclinical evidence supports a mechanism through which aspirin may exert antineoplastic effects. Aspirin irreversibly inhibits COX enzymes, which convert arachidonic acid into various prostaglandins.[13] COX-2 drives the production of PGE2, which has been implicated in tumor growth through a multitude of downstream effects, including the promotion of cellular proliferation and motility, the

Table 2. *Multivariable Cox proportional hazards analysis of factors associated with death after radical cystectomy accounting for aspirin dose*

	Distant Metastasis		Ca Specific Mortality		All Cause Mortality	
	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Age/10-yr increase	1.14 (0.98–1.34)	0.09	1.14 (0.99–1.31)	0.07	1.21 (1.06–1.37)	0.004
ECOG 0, 1, 2+	1.12 (0.86–1.46)	0.38	1.23 (0.99–1.54)	0.07	1.38 (1.15–1.65)	0.001
Body mass index	0.99 (0.97–1.02)	0.41	0.97 (0.95–0.99)	0.01	0.97 (0.95–0.99)	0.01
Aspirin use:						
None	Referent	—	Referent	—	Referent	—
Low dose (25/81/162 mg)	0.89 (0.67–1.20)	0.45	0.61 (0.46–0.81)	<0.001	0.62 (0.49–0.80)	<0.001
High dose (325/650 mg)	1.32 (0.82–2.12)	0.26	0.84 (0.53–1.34)	0.47	0.85 (0.57–1.26)	0.42
Other use:						
Metformin	1.34 (0.77–2.32)	0.30	0.80 (0.46–1.39)	0.43	0.78 (0.49–1.24)	0.29
Statin	1.12 (0.84–1.50)	0.45	1.16 (0.88–1.53)	0.29	1.11 (0.88–1.40)	0.40
Pathological T stage:						
Less than T2	Referent	—	Referent	—	Referent	—
T2	1.93 (1.26–2.96)	0.002	1.89 (1.26–2.83)	0.002	1.45 (1.05–2.00)	0.02
T3/4	5.53 (3.96–7.72)	<0.001	5.59 (4.07–7.69)	<0.001	3.63 (2.81–4.69)	<0.001
Pathological node pos	2.56 (1.87–3.51)	<0.001	3.02 (2.26–4.03)	<0.001	2.85 (2.19–3.70)	<0.001
Periop blood transfusion	1.30 (0.98–1.71)	0.07	1.71 (1.31–2.22)	<0.001	1.74 (1.39–2.18)	<0.001

Adjusted for gender, history of coronary artery disease/myocardial infarction, peripheral vascular disease, congestive heart failure, diabetes, smoking, neoadjuvant chemotherapy, adjuvant chemotherapy, diversion type, pathological carcinoma in situ, total number of lymph nodes removed, positive surgical margin and estimated blood loss.

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enhancement of angiogenesis, the inhibition of apoptosis and the suppression of antitumor immunity.[1] In animal models several investigators have observed that PGE2 promotes urothelial carcinogenesis[6,14] and in fact may also be responsible for inducing resistance to cytotoxic chemotherapy.[15,16]

Although selective COX-2 inhibitors have demonstrated activity against urothelial cancer in vitro,[17] concerns about cardiovascular morbidity have hindered clinical use.[18] However, the nonselective COX inhibitor aspirin, which is widely used for its cardioprotective effects,[5] might similarly exert an effect against urothelial cancer via COX-2 inhibition.

Clinical evidence in support of aspirin use for bladder cancer has been previously shown in the setting of NMIBC treated with BCG. These data support our observation of increased OS and CSS among aspirin users with pathological NMIBC after RC. In a study of 43 patients receiving BCG Gee et al observed a 64% 5-year recurrence-free survival rate in aspirin users compared to 27% in nonusers.[8] A significant association between aspirin use and a decreased recurrence risk was maintained after multivariable adjustment. Likewise, Boorjian et al noted that a significantly decreased risk of progression to RC (HR 0.71) was associated with aspirin use in 907 patients receiving BCG for NMIBC.[7] COX-2 inhibition has been shown to hinder the ability of urothelial tumors to induce T cell dysfunction, partly through down-regulating PD-L1 expression, which has been suggested as a potential mechanism underlying these findings.[19–21]

The results of the presented subset analyses suggest that a beneficial effect of aspirin may be confined to patients with NMIBC. It is possible that aspirin users with NMIBC had lower PD-1/PD-L1 expression via the mentioned mechanism, effectively inhibiting progression and leading to the observed survival advantage compared to nonaspirin users. Conversely the absence of a similar survival difference in patients with muscle invasive disease may reflect that aspirin has less of an effect on muscle invasive tumors, perhaps suggesting that the impact of aspirin on immune tolerance pathways has been overcome at this stage.

Further, despite the significant association of aspirin use with OS and CSS, we did not note a corresponding decrease in disease recurrence. This may reflect the fact that recurrence and progression are unreliable end points for agents impacting immune tolerance. Indeed, randomized data comparing pembrolizumab to second line chemotherapy in metastatic urothelial carcinoma cases revealed that pembrolizumab led to significant improvement in OS, although there was no difference in progression-free survival.[22] Alternatively this could stem from the inability of our data abstraction to comprehensively capture tumor recurrence as reliably as mortality end points. Further work is needed to clarify these findings.

As with any observational study we must acknowledge that the presented data do not confirm the existence of a causal pathway. However, the current analysis meets several criteria set forth by Hill to support the existence of causal relationships in observational research.[23] The observed effect size was large (HR 0.64), indicating a strong level of association between aspirin use and CSS. Temporality is met in that the exposure (preoperative daily aspirin use) reliably preceded the outcome (survival after RC). The existence of a plausible biological mechanism by which aspirin reduces cancer activity supports the notion of causality. Moreover, there is coherence between clinical findings and in vitro evidence. The latter has demonstrated that COX-2 inhibition decreases the growth of urothelial cancer cells.[17,24] The principle of reproducibility is partially met, given previous observations of a benefit to daily aspirin in NMIBC.[7,8] However, our findings require external validation.

Another Hill criterion is a dose-response relationship with greater exposure leading to a change in risk.[23] In the current study we observed a survival advantage to low but not high dose aspirin. This finding is consistent with data in the colorectal cancer literature. Two randomized trials comparing low (81 to 162 mg) and high (300 to 325 mg) aspirin doses confirmed a benefit to prevent recurrent colorectal adenomas only for the low dose regimen.[12] That finding renders it less likely that our results are purely a consequence of selection bias. Higher aspirin doses also lead to greater suppression of PGEs other than PGE2, of which many have anticancer properties that could override any potential benefit of low dose aspirin.[25] Further investigation is necessary to corroborate the validity of this finding.

We recognize that a major limitation of the presented data is the absence of information on patients who began using aspirin postoperatively, when urologists would have the opportunity to influence use. Our data set did not capture new medication use after the index procedure. Therefore, the presented data should be viewed as hypothesis generating. Assessment of the impact of postoperative aspirin use is required before aspirin can be recommended in an adjuvant manner.

Given the retrospective design of our study, we also acknowledge that the reported findings may be due to selection bias/unmeasured confounding. For example, in patients on daily aspirin other behaviors may have been responsible for improved

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survival. We attempted to account for this in part by adjusting for concurrent statin and metformin use, which are indicative of engagement with a health care provider.[26]

We acknowledge as well the absence of information on the duration of preoperative aspirin use, which inhibited us from ascertaining the effect that duration of use may have had on outcomes. Notably we presumed the postoperative resumption of aspirin. However, it is likely reasonable to assume that patients received aspirin with high fidelity, given that an 82% adherence rate to recommended daily aspirin has been observed among adults 40 years old or older in the United States.[27] In addition, data on other nonsteroidal anti-inflammatory medications were not collected and routine use of these medications may have influenced results.

Despite these limitations we believe that the association between preoperative aspirin use and improved survival after RC is a novel observation. Concordance between these findings and those in several other malignancies indicate that the reported results may not be completely explained by chance. If these results can be validated prospectively, aspirin may deserve consideration as a low cost, low morbidity treatment adjunct in patients who require RC. A future trial randomizing patients after RC to aspirin or placebo would provide level 1 evidence to inform such therapy. It could be designed to include translational (ie differences in serum cytokine levels) and clinical (recurrence and survival) end points.

CONCLUSIONS

We found that preoperative aspirin use was associated with lower cancer specific and all cause mortality following RC for bladder cancer, consistent with reported data on other malignancies. Determining whether this association represents a causal relationship and identifying the potential underlying biological mechanisms require further study.

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