ISSN: 2693-4965
DOI: 10.33552/OJCRR.2026.08.000688
Online Journal of Cardiology Research & Reports
Iris Publishers

Review Article

Association Between Statin Use and Long-term Survival Outcomes in Patients with Non-muscle-invasive Bladder Cancer: A Systematic Review

Hatice Firat Başaranoğlu[1], Mert Başaranoğlu[2]*, Cansu Nebioğlu[3], and Ali Nebioğlu[4]

[1]*Department of Internal Medicine, Mersin University Faculty of Medicine, Mersin, Turkey*

[*2]*Department of Urology, Mersin University Faculty of Medicine, Mersin, Turkey*

[3]*Department of Pathology, Mersin University Faculty of Medicine, Mersin, Turkey*

[4]*Department of Urology, Mersin City Hospital, Mersin, Turkey*

***Corresponding author:** Mert Başaranoğlu, MD, Department of Urology, Mersin University Faculty of Medicine, Çiftlikköy Kampüsü, 33343 Mersin, Turkey

Received Date: June 18, 2026

Published Date: June 29, 2026

Abstract

Background: Non-muscle-invasive bladder cancer (NMIBC) represents 75–80% of all bladder cancers and is characterized by high recurrence (50–70%) and progression (10–30%) rates. Statins (HMG-CoA reductase inhibitors), widely prescribed for cardiovascular prevention, exert pleiotropic anti-tumor effects including pro-apoptotic, anti-proliferative, and immunomodulatory activities, suggesting potential benefit in oncologic settings.

Methods: A systematic PubMed/MEDLINE search was conducted on June 17, 2026, using structured queries across 10 search categories encompassing NMIBC, statins, survival, recurrence, and progression. PRISMA 2020 guidelines were followed throughout. Observational studies reporting statin use and at least one long-term survival endpoint in histologically confirmed NMIBC patients were eligible. Preclinical studies, case reports, and muscle-invasive bladder cancer (MIBC)-only studies were excluded.

Results: From 4,133 identified records, 11 observational studies and secondary analyses comprising 29,370 NMIBC patients met all inclusion criteria. Follow-up ranged from 31 months to 11.3 years. Three studies reported improved overall survival (OS) with statin use (hazard ratio [HR] range: 0.607–0.93), and one reported improved cancer-specific survival (CSS; HR 0.571, 95% CI 0.376–0.868). Reduced tumor recurrence was observed in two studies (Ferro et al.: HR 0.80, 95% CI 0.67–0.95; Strobach et al.: HR 0.12, 95% CI 0.01–0.97 on multivariate analysis). Conversely, five studies found no statistically significant association with CSS, RFS, or progression-free survival (PFS), and one reported increased recurrence rates in statin users. Marked heterogeneity was observed across studies in statin type, timing, dose, treatment modality, and follow-up duration.

Conclusions: Evidence regarding statin use and NMIBC survival outcomes is inconsistent. A modest OS benefit, particularly with pre-BCG statin initiation, is suggested by larger studies; however, CSS, RFS, and PFS improvements are not consistently demonstrated. Prospective randomized trials with standardized statin protocols and NMIBC-specific outcome reporting are needed.

Keywords: Non-muscle-invasive bladder cancer; NMIBC, statins; HMG-CoA reductase inhibitors; recurrence-free survival; overall survival; cancer-specific survival; systematic review; BCG immunotherapy; pleiotropic effects

Abbreviations: NMIBC: Non-muscle-invasive bladder cancer; MIBC: Muscle-invasive bladder cancer; CIS: Carcinoma in situ; BCG: Bacillus Calmette-Guérin; TURBT: Transurethral resection of bladder tumor; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; RFS: Recurrence-free survival; PFS: Progression-free survival; OS: Overall survival; CSS: Cancer-specific survival; DFS: Disease-free survival; HR: Hazard ratio; CI: Confidence interval; RR: Relative risk; OR: Odds ratio; RCT: Randomized controlled trial; EAU: European Association of Urology; EORTC: European Organisation for Research and Treatment of Cancer; TNBC: Triple-negative breast cancer; VEGF: Vascular endothelial growth factor; COX-2: Cyclooxygenase-2; PPARγ: Peroxisome proliferator-activated receptor gamma; EMT-Epithelial-mesenchymal transition; cGAS: STING-Cyclic GMP: AMP synthase–stimulator of interferon genes; BMI: Body mass index; NOS: Newcastle-Ottawa Scale; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Introduction

Non-muscle-invasive bladder cancer (NMIBC) - encompassing pathological stages Ta, T1, and carcinoma in situ (CIS) - accounts for approximately 75–80% of all newly diagnosed bladder cancers, a malignancy ranking among the ten most frequently diagnosed solid tumors globally and the most costly to manage per patient over a lifetime. NMIBC is predominantly a disease of older adults, with a male-to-female incidence ratio of approximately 3-4:1, and carries a disproportionate clinical burden driven by characteristically high recurrence rates [1]. In prospective series and multicenter registry studies, histologically confirmed tumor recurrence occurs in 35–54% of NMIBC patients undergoing transurethral resection of the bladder tumor (TURBT) with or without adjuvant intravesical therapy [2,3], with outcomes influenced by tumor grade, stage, multiplicity, and the presence of concomitant carcinoma in situ. Disease progression to muscle-invasive cancer is observed in approximately 10-13% of patients [2,4], and early recurrence within three months of initial resection independently predicts inferior progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS) [4], highlighting the critical clinical importance of sustained oncologic control. Standard management consists of TURBT followed by risk-stratified intravesical therapy; in intermediate and high-risk disease, adjuvant intravesical Bacillus Calmette-Guérin (BCG) immunotherapy yields five-year recurrence-free survival rates of approximately 61% and overall survival exceeding 90% in favorable cohorts [5]. Nevertheless, BCG failure occurs in up to 40% of high-risk patients, recurrence remains common even after adequate immunotherapy, and the cumulative burden of repeated surveillance and retreatment significantly impairs quality of life and inflates healthcare resource utilization [6]. This therapeutic ceiling—coupled with the absence of a validated pharmacological adjunct proven to improve long-term survival across all NMIBC risk categories—has motivated investigation of co-administered agents with potential pleiotropic anti-tumor activity.

Statins (3-hydroxy-3-methylglutaryl coenzyme-A [HMG-CoA] reductase inhibitors), prescribed globally for the management of hyperlipidemia and cardiovascular risk reduction, exert a diverse spectrum of pleiotropic biological effects that extend well beyond cholesterol biosynthesis inhibition. Through suppression of the mevalonate pathway, statins reduce the availability of farnesyl pyrophosphate and geranylgeranyl pyrophosphate—isoprenoid intermediates required for post-translational prenylation of small GTPases including Ras, Rho, and Rac—thereby attenuating downstream pro-tumorigenic signaling governing cellular proliferation, invasion, and metastasis. Additional oncologically relevant mechanisms include: (i) activation of mitochondrial apoptotic pathways via reactive oxygen species generation and cytosolic mitochondrial DNA sensing through the cGAS-STING signaling axis [7]; (ii) downregulation of NF-κB-dependent transcription and suppression of pro-inflammatory cytokines—interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)—that contribute to chronic inflammation-driven carcinogenesis [8]; (iii) anti-angiogenic activity through vascular endothelial growth factor (VEGF) pathway modulation; and (iv) immunomodulatory effects including MHC class II upregulation and enhancement of T-cell-mediated anti-tumor immune surveillance. Within the urological cancer context specifically, statins have been shown to inhibit renal cell carcinoma cell growth by suppressing AKT, mTOR, and ERK phosphorylation and reducing tumor cell motility in a dose- and time-dependent manner [9]. In a chemically induced rat model of bladder carcinogenesis, atorvastatin demonstrated chemo preventive activity through COX-2 downregulation and inhibition of lipid peroxidation [10]. Lipophilic statins (simvastatin, atorvastatin, lovastatin) penetrate cellular membranes more efficiently than hydrophilic counterparts (pravastatin, rosuvastatin), conferring potentially greater intracellular anti-tumor potency. At the clinical epidemiological level, a meta-analysis synthesizing 60 observational studies encompassing 953,177 cancer patients demonstrated that statin use was associated with a significant reduction in cancer-specific mortality (hazard ratio [HR] 0.78, 95% CI 0.74–0.84) and improvement in recurrence-free survival (HR 0.87, 95% CI 0.78–0.97) across multiple tumor types [11], providing broad population-level support for the translational investigation of statins in solid tumor oncology.

Despite this compelling pharmacological rationale, epidemiological studies focusing on the relationship between statin use and bladder cancer incidence have produced consistently neutral results. A meta-analysis of 13 studies—including three randomized controlled trials, five cohort studies, and five case-control studies—found no significant association between statin use and overall bladder cancer risk (relative risk [RR] 1.07, 95% CI 0.95–1.21) [12], corroborated by a population-based case-control study of 325 incident cases from Taiwan (adjusted odds ratio [OR] 0.88, 95% CI 0.61–1.25) [13]. The clinically more pertinent question—whether statins modify long-term survival outcomes in patients with established NMIBC—has received comparatively less systematic attention, and the observational evidence addressing it is substantially conflicting. Richard et al. found that cumulative post-diagnosis statin use improved overall survival (HR 0.93 per year of use, 95% CI 0.91–0.96) but not cancer-specific survival in a population-based cohort of 13,811 elderly Canadians with NMIBC [14]. Liu et al. subsequently identified significant protective effects on both OS and CSS exclusively among patients who initiated statin therapy prior to BCG immunotherapy (OS HR 0.607, 95% CI 0.514–0.716; CSS HR 0.571, 95% CI 0.376–0.868) [15]. In contrast, Crivelli et al. reported no association between statin use at diagnosis and any survival endpoint in a multicenter cohort of 1,117 NMIBC patients across three institutions [16]. The most comprehensive systematic review to date, encompassing 32 studies of all bladder cancer stages, concluded that statins exert a neutral effect on local control, recurrence, survival, and BCG efficacy [17]—but critically, it did not restrict analysis to NMIBC, did not examine the moderating role of statin timing, type, dose, or duration relative to intravesical therapy, and predates the largest observational series published in this area. These evidence gaps—an exclusively NMIBC-focused synthesis using contemporary data, with attention to BCG-timing interactions and statin-specific effects - have not yet been addressed.

To fill this gap, we conducted a systematic review adhering to PRISMA 2020 guidelines to identify, critically appraise, and synthesize all published evidence evaluating the association

between statin use and long-term survival outcomes in adults with histologically confirmed NMIBC. The following pre-specified research questions were addressed: (i) Is statin use associated with improved OS, CSS, recurrence-free survival (RFS), or PFS in NMIBC patients? (ii) Does the timing of statin initiation relative to intravesical BCG therapy modify the observed association? (iii) Are there meaningful differences attributable to statin type (lipophilic vs. hydrophilic), dose, or duration of use? (iv) Does concomitant statin use interact with BCG immunotherapy efficacy? Systematic characterization of methodological heterogeneity across studies and identification of priorities for prospective research constituted additional pre-specified objectives.

Discussion

Search Strategy

A systematic literature search was performed in PubMed/MEDLINE in June 2026. Ten structured search category queries were constructed encompassing the following domains: core NMIBC and statin survival associations; statin-specific agents and bladder cancer; NMIBC and statin recurrence or progression; statin and bladder cancer mortality; statin cancer mechanisms and pleiotropic effects; systematic reviews and meta-analyses; NMIBC epidemiology and prognosis; statin observational studies; statin-BCG interaction; and NMIBC risk factors and comorbidities. Representative search strings included combinations of Medical Subject Headings and free-text terms such as "non-muscle-invasive bladder cancer," "NMIBC," "statin," "statins," "HMG-CoA reductase inhibitor," "survival," "overall survival," "cancer-specific survival," "progression-free survival," "disease progression," "prognosis," and "survival outcomes." No date, language, or publication-type filters were applied during database retrieval to maximize sensitivity. A total of 4,133 records were identified. Results were stored in JSON format with automated relevance scoring and deduplication.

Eligibility Criteria

Studies were included if they met the following criteria: adult patients aged 18 years or older with histologically confirmed NMIBC (stages Ta, T1, or carcinoma in situ); documented statin use of any type, dose, or duration compared with non-use; at least one long-term survival endpoint reported, including recurrence-free survival, progression-free survival, overall survival, or cancer-specific survival, with hazard ratios, odds ratios, or risk ratios accompanied by 95% confidence intervals; retrospective or prospective cohort design, case-control design, or secondary analysis of randomized controlled trials with a statin exposure arm; and publication in English. Studies were excluded if they were restricted to muscle-invasive bladder cancer without an NMIBC-specific subgroup analysis; focused exclusively on upper tract urothelial carcinoma; were preclinical studies including in vitro cell line experiments or animal models; were case reports, editorials, letters, conference abstracts, or narrative reviews; did not report survival outcomes or reported only cancer incidence as an endpoint; or had insufficient data to determine statin exposure or extract outcome estimates.

Study Selection

Two investigators independently screened all 4,133 titles and abstracts against eligibility criteria. Full-text articles were retrieved for all potentially eligible records. Disagreements were resolved by consensus. The selection process is summarized in the PRISMA 2020 flow diagram (Figure 1).

Data Extraction

Data were extracted independently into a structured form capturing: first author and year; country and data source; study design; patient inclusion dates; total sample size and number of statin users; NMIBC stage and grade; treatment modality (TURBT, BCG, intravesical chemotherapy); statin type, dose, and timing relative to diagnosis or treatment; median follow-up duration; survival outcomes assessed; key quantitative results (HRs, 95% CIs, p-values); and adjustment variables.

Quality Assessment

Methodological quality of included cohort and case-control studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates selection (0-4 stars), comparability (0-2 stars), and outcome/exposure (0-3 stars). Studies scoring ≥7 stars were considered high quality.

Search Results

The database search identified 4,133 records (Figure 1). After title and abstract screening, 4,070 records were excluded due to irrelevance to the NMIBC + statin + survival topic (wrong study population, non-clinical studies, wrong outcomes, reviews). Sixty-three records were assessed as full text. After applying inclusion and exclusion criteria, 11 studies were eligible for inclusion in the qualitative synthesis. Reasons for full-text exclusion (n=52): MIBC only/no NMIBC subgroup (n=15); UTUC (n=8); preclinical in vitro/animal studies (n=14); no survival endpoint (n=8); bladder cancer incidence only, not survival (n=2); reviews/editorials retained as contextual reference (n=5).

Study Characteristics

The 11 included studies were published between 2009 and 2025 and enrolled a combined 29,370 patients. Nine were retrospective observational studies; one was a prospective monocentric cohort [18]; one was a secondary analysis of an RCT database [19]. Study characteristics are summarized in Table 1.

Main Outcomes

Overall Survival (OS)

Multiple studies reported OS as an endpoint [14-16,20-23]. Three demonstrated statistically significant OS benefit associated with statin use. Liu et al. reported that 'statins before BCG' was an independent protective factor for OS (HR 0.607, 95% CI 0.514–0.716) in multivariable Cox regression on a cohort of 2,602 patients with a median follow-up of 11 years [15]. Ndukwe et al., using the national Veterans Affairs database (n=8,814), found statins associated with improved OS (HR 0.89, 95% CI 0.83–0.96, p=0.002) after inverse propensity score-weighted adjustment [20]. Richard et al. observed that each additional year of cumulative statin use after NMIBC diagnosis was associated with a 7% reduction in all-cause mortality (HR 0.93, 95% CI 0.91–0.96) [14]. By contrast, Crivelli et al., Brooks et al., Singla et al., and Skolarus et al. reported no significant OS benefit [16,21-23].

Cancer-Specific Survival (CSS)

Four studies reported CSS [14–16,20]. Liu et al. found that pre-BCG statin use was independently associated with improved CSS (HR 0.571, 95% CI 0.376–0.868) [15]. Neither Richard et al. (p=0.10) nor Ndukwe et al. (HR 0.88, p=0.09) reached statistical significance for CSS, and Crivelli et al. found no association (p>0.05) [14,16,20].

Recurrence-Free Survival (RFS)

Nine studies reported recurrence or RFS [15,16,19-25]. Ferro et al. identified an independent protective association between statin use and tumor recurrence (HR 0.80, 95% CI 0.67–0.95, p=0.009) in 1,510 T1 high-grade NMIBC patients at 18 Italian centers, with median RFS extending from 47 to 53 months with statin use [24]. Strobach et al. in a prospective cohort of 52 first-diagnosis BC patients, also found statins to be an independent protective factor for RFS on multivariate Cox regression (HR 0.12, 95% CI 0.01–0.97, p=0.047), though the wide confidence interval reflects the small sample size [18]. In contrast, Pastore et al. reported a paradoxical increase in recurrence among statin users (61.5% vs 46.3%, p=0.01) [25]. Six studies found no significant association with recurrence [15,16,19-21,23].

Progression-Free Survival (PFS)

PFS was reported in six studies [15,16,20-22,24]. None demonstrated a statistically significant independent benefit of statin use on PFS in multivariable analysis. Liu et al. noted a significant Kaplan-Meier separation favoring the statin group (p<0.001) but this did not reach significance in Cox regression (HR 0.689, 95% CI 0.469-1.013, p=0.065) [15].

Interpretation

This systematic review synthesized evidence from 11 observational studies enrolling a combined 29,370 NMIBC patients, representing the most comprehensive NMIBC-specific analysis of statin use and survival outcomes available in the current literature (Table 1; Figure 1). The principal finding is that the available evidence is inconsistent and insufficient to support a uniform survival benefit of statin use across all NMIBC survival endpoints. Three studies demonstrated a statistically significant OS benefit [14,15,20], and one identified improved CSS restricted to patients initiating statins prior to BCG immunotherapy (HR 0.571, 95% CI 0.376–0.868) [15] the only such CSS signal in the NMIBC literature and one that must be interpreted cautiously given its derivation from a post-hoc subgroup of an observational cohort. With respect to tumor recurrence, the independent protective association observed by Ferro et al. in 1,510 T1 high-grade NMIBC patients (HR 0.80, 95% CI 0.67–0.95, p=0.009) [24], and corroborated - albeit imprecisely - by the prospective cohort of Strobach et al. (multivariable HR 0.12, 95% CI 0.01–0.97) [18], stands in direct opposition to the paradoxical increase in recurrence reported by Pastore et al. (61.5% vs. 46.3%, p=0.01) [25]. Progression-free survival was not significantly modified by statin use in any of the studies reporting this endpoint [15,16,20–22,24], and BCG immunotherapy efficacy was not impaired by concurrent statin administration in the three studies specifically addressing this interaction [19,21,23]. Taken together, these findings indicate that statins are pharmacologically safe to administer alongside BCG immunotherapy but do not consistently alter tumor biology at doses used in routine clinical practice.

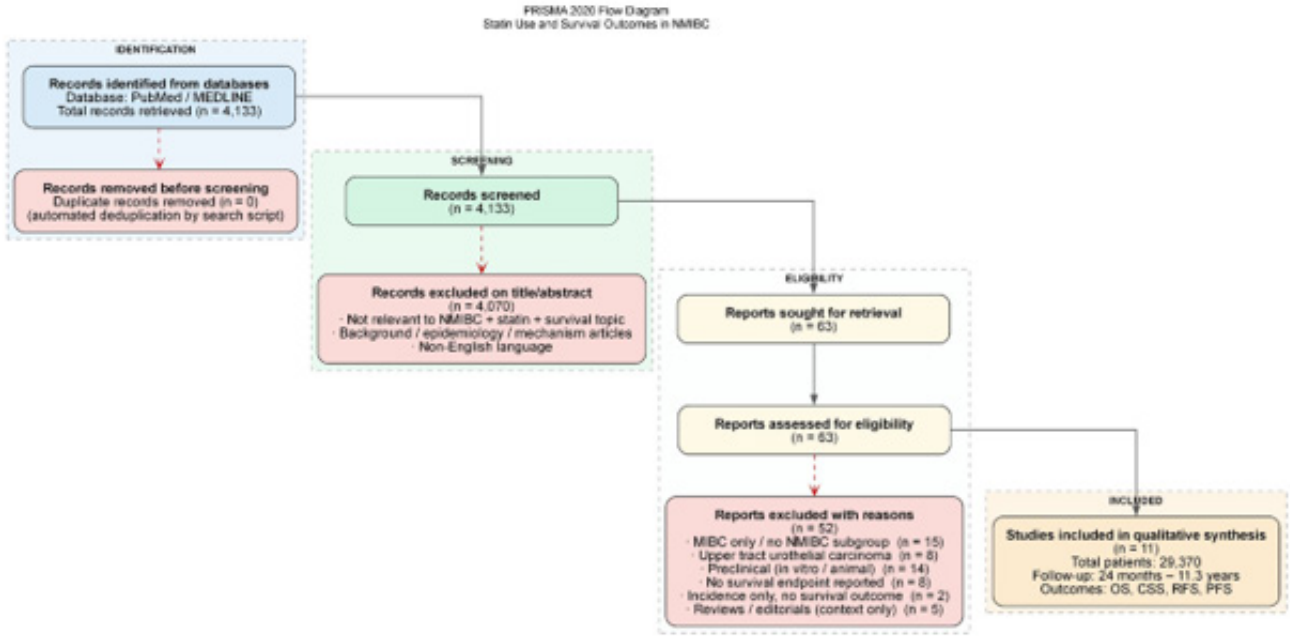

Figure 1: PRISMA 2020 flow diagram for the systematic literature search on statin use and survival outcomes in non-muscle-invasive bladder cancer. The diagram illustrates the identification, screening, eligibility, and inclusion phases of study selection from PubMed/MEDLINE (search date: June 2026).

Table 1: Characteristics of studies included in the systematic review.

#	Author (Year)	Design	Country	N Total / Statin Users (%)	NMIBC Stage	Treatment	Statin Type / Timing	Follow-up (Median)	Outcomes	Key Results
1	Liu K et al. (2025) [15]	Retrospective multicenter cohort	International	2,602 / NR	All stages (BCG-eligible)	TURBT + intravesical BCG	Any statin; pre-BCG vs post-BCG subgroups	11.0 years	OS, CSS, RFS, PFS	Pre-BCG statins: OS HR 0.607 (0.514–0.716); CSS HR 0.571 (0.376–0.868); no RFS or PFS benefit on multivariate analysis
2	Ndukwe E et al. (2025) [20]	Retrospective cohort (VA database)	USA	8,814 / 3,349 (38%)	Early-stage NMIBC	BCG (≥6 months)	Any statin, ≥6 months concurrent with BCG	11.3 years	Recurrence, secondary events, CSS, OS	Improved OS (HR 0.89, 95% CI 0.83–0.96, p=0.002); no CSS (HR 0.88, p=0.09), recurrence (HR 1.05, p=0.23) benefit
3	Richard PO et al. (2017) [14]	Population-based retrospective cohort	Canada	13,811 / 4,748 (34%)	NMIBC (age ≥66 years)	Not specified	Any statin; cumulative daily dose calculated	7.1 years	CSS, OS	No CSS improvement (p=0.10); cumulative statin use associated with better OS (HR 0.93 per year of use, 95% CI 0.91–0.96)
4	Singla N et al. (2017) [21]	Retrospective single-center	USA	99 / 64 (65%)	High-grade NMIBC	BCG induction (≥1 course)	Any statin (included in anti-inflammatory group)	31.4 months	Recurrence, progression, CSS, OS	Anti-inflammatory use (including statins) not independently predictive of any outcome on multivariate Cox analysis
5	Ferro M et al. (2021) [24]	Retrospective multicenter (18 centers)	Italy	1,510 / 402 (26.6%)	T1 high-grade NMIBC	TURB (± BCG)	Any statin, daily intake	NR	Residual tumor (re-TURB), RFS, PFS, OS	Lower recurrence risk (HR 0.80, 95% CI 0.67–0.95, p=0.009); RFS 47 vs 53 months; no PFS or OS benefit; higher HG residual at re-TURB (OR 1.37, p=0.022)
6	Brooks NA et al. (2021) [22]	Retrospective institutional cohort	USA	579 / 243 (42%)	NMIBC (90% HG; 47.2% T1)	BCG induction	Any statin	4.6 years	RFS, PFS, CSS, OS	No significant association between statins and any survival outcome
7	Pastore A et al. (2015) [25]	Retrospective single-center	Italy	574 / 91 statin group	All NMIBC (Ta, T1, Tis)	TURB	Statin ≥20 mg/day for ≥2 years	45.1 months	Recurrence (RFS)	Statin use was independent risk factor for recurrence (61.5% vs 46.3%, p=0.01); aspirin showed protective effect
8	Crivelli JJ et al. (2013) [16]	Retrospective multicenter (3 centers)	USA/ International	1,117 / 341 (30.5%)	All NMIBC (primary + recurrent)	TURBT ± BCG	Any statin at time of diagnosis	62.7 months	Recurrence, progression, CSS, OS	No association with any endpoint (all p>0.05); BCG efficacy unaffected by statin use
9	Skolarus TA et al. (2009) [23]	Retrospective single-center (VA)	USA	90 / 43 (47.8%)	NMIBC	BCG	Any statin, concurrent with BCG	NR	Tumor progression, total recurrences, disease-specific mortality, OS	No significant differences between statin and non-statin groups for any outcome
10	Wang Z et al. (2022) [19]	Secondary analysis of RCT database	Singapore	122 / NR	NMIBC	BCG (RCT)	Any statin	102 months	OS, DSS, recurrence, progression	Statins not associated with disease recurrence or progression
11	Strobach D et al. (2023) [18]	Prospective monocentric observational	Germany	52 FD-BC / NR	BC first diagnosis (predominantly NMIBC)	TURBT	Any chronic statin (ATC-coded)	24 months	RFS, CSS	Statins: positive effect on RFS in univariate (p=0.025) and multivariate analysis (HR 0.12, 95% CI 0.01–0.97, p=0.047); no CSS benefit

Table Abbreviations: BCG: Bacillus Calmette-Guérin; CSS: cancer-specific survival; DSS: disease-specific survival; HG: high-grade; HR: hazard ratio; NR: not reported; NMIBC: non-muscle-invasive bladder cancer; OR: odds ratio; OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial; RFS: recurrence-free survival; TURB/TURBT: transurethral resection of bladder/bladder tumor; VA: Veterans Affairs.

The inconsistency documented in NMIBC statin research mirrors the broader pattern observed across other solid tumors, though with important disease-specific differences that may explain why bladder-cancer–specific benefit is less reproducible. In breast cancer—the tumor type with the most extensive statin observational literature—a meta-analysis of 31 cohort studies comprising 261,834 patients demonstrated that post-diagnosis statin use was associated with significantly reduced cancer-specific mortality (HR 0.76, 95% CI 0.67–0.87) and reduced recurrence (HR 0.71, 95% CI 0.61–0.82) [26]. A focused meta-analysis in triple-negative breast cancer (TNBC)—the subtype most analogous to high-grade NMIBC in its reliance on non-hormonal treatment—found concurrent statin use associated with improved 5-year disease-free survival (OR 1.44, 95% CI 1.04–1.98) but not overall survival [27]. Across all cancer types, statin use was associated with reduced cancer-specific mortality (HR 0.78) and improved RFS (HR 0.87), but not PFS (HR 1.05) [11], suggesting that anti-recurrence effects, where present, do not necessarily translate into local tumor control benefits—a pattern consistent with the NMIBC findings. A key contextual distinction is that NMIBC treated with BCG involves a complex urothelial innate immune response; statins' dual pro- and anti-inflammatory properties may therefore interact with BCG in ways that differ qualitatively from their interaction with systemic cytotoxic chemotherapy in breast or colorectal cancer. The systematic review by Symvoulidis et al. encompassing all bladder cancer stages without BCG-stratified subgroup analyses—concluded a neutral effect overall [17]; the present review's restriction to NMIBC and explicit attention to BCG timing addresses this limitation directly.

The biological plausibility for statin-mediated survival benefit in NMIBC is supported by multiple converging molecular mechanisms. Through inhibition of farnesyl pyrophosphate and geranylgeranyl pyrophosphate synthesis, statins prevent post-translational prenylation of Ras and Rho GTPases, attenuating the NF-κB, AKT, and ERK signaling cascades that drive NMIBC cell proliferation, survival, and invasion [8,9,28]. A window-of-opportunity clinical trial administering simvastatin 20 mg/day for 2–4 weeks between breast cancer diagnosis and surgery demonstrated in situ upregulation of the cell cycle inhibitor p27 (fold change 3.2, p=0.025), pro-apoptotic cleaved caspase-3 (fold change 2.1, p=0.016), and cyclin D1 in tumor tissue—confirming that pharmacologically achievable statin concentrations engage apoptotic and cell cycle arrest pathways within the tumor microenvironment [29]. The apoptotic pathway is further activated via mitochondrial dysfunction, reactive oxygen species generation, and engagement of the cGAS-STING innate immune sensing pathway, triggering type-I interferon responses and caspase activation as demonstrated in colorectal cancer cells with lovastatin [7]. Additional mechanisms include Wnt/β-catenin pathway suppression via reciprocal SATB1 downregulation and SATB2 upregulation [30], Rac1 GTPase inhibition sensitizing tumor cells to statin-induced apoptosis at clinically relevant concentrations [31], and suppression of KRAS prenylation with downstream upregulation of pro-apoptotic PUMA, inhibition of surviving/XIAP/Bcl-2 anti-apoptotic proteins, and enhanced chemosensitivity [28]. In the bladder-specific context, statin administration in an ischemia-induced overactive bladder model restored microvascular density, suppressed mucosal IL-6 and IL-8 expression, and attenuated arteriosclerotic wall thickening [32] suggesting that statins may also attenuate the ischemic and pro-inflammatory bladder microenvironment that facilitates mucosal carcinogenesis and recurrence. In vitro, atorvastatin exerted chemo preventive activity in a chemically-induced bladder carcinogenesis model via COX-2 suppression and PPARγ-mediated anti-inflammatory signaling [10]. The net effect of these mechanisms on BCG-mediated immune activation—which depends on innate urothelial immune signaling, neutrophil and macrophage recruitment, and T-lymphocyte priming—warrants dedicated experimental investigation, as statins may both synergize with BCG through MHC-II upregulation and T-cell facilitation, and potentially blunt the pro-inflammatory signal required for full BCG efficacy.

A major unresolved question is whether statin type, dose, and duration of use meaningfully determine oncologic outcomes in NMIBC—a question none of the 11 included studies was adequately designed to address. All but one study (Pastore et al., who required ≥20 mg/day for ≥2 years [25]) classified exposure as any statin versus no statin, conflating lipophilic agents (simvastatin, atorvastatin, lovastatin) with hydrophilic counterparts (pravastatin, rosuvastatin) that differ substantially in cellular penetrability and intracellular anti-tumor potency. Evidence from breast cancer provides indirect but instructive guidance: a meta-analysis of 14 studies found that lipophilic statin use was independently associated with improved recurrence-free survival (HR 0.72, 95% CI 0.59–0.89), whereas hydrophilic statin use was not statistically significant (HR 0.80, 95% CI 0.44–1.46) [33]. An updated 2025 meta-analysis incorporating immortal-time bias-adjusted subgroup analyses confirmed that lipophilic statins conferred greater protection for both breast cancer death and recurrence than hydrophilic agents [34]. The differential penetrability of lipophilic statins into the urothelial compartment—an epithelium with limited active transport compared to liver—makes this distinction biologically plausible for NMIBC. A further nuance from breast cancer data is that statin use was associated with a significant reduction in distant cancer recurrence (HR 0.86, 95% CI 0.80–0.94) but not loco-regional recurrence (HR 0.97) [35], suggesting a preferential anti-metastatic mechanism through EMT inhibition rather than direct anti-local recurrence activity. In NMIBC, where intraluminal local recurrence is the dominant clinical failure mode, this distinction may partly explain why RFS improvements are not consistently observed despite plausible anti-metastatic mechanisms. Future NMIBC studies should mandate prospective collection of statin agent identity, cumulative defined daily doses (DDDs), continuous use duration, and initiation timing relative to both TURBT and BCG.

The present review identifies both reproducible signals and irreconcilable contradictions in the NMIBC statin literature that require explicit discussion. The OS benefit observed across three independent populations spanning two decades and three continents [14,15,20] constitutes the most reproducible finding and is broadly consistent with the pan-cancer OS signal (HR 0.78)

[11]; however, whether this reflects a bladder-cancer–specific anti-tumor effect or a cardiovascular survival advantage in an elderly, multimorbid population cannot be resolved from observational data—particularly since Richard et al. found no CSS benefit despite a significant OS benefit [14]. This cardiovascular confounding is not unique to NMIBC: in colorectal cancer surgery, statin use is consistently associated with reduced 30-day postoperative mortality through cytoprotective and anti-inflammatory perioperative mechanisms [36], rather than through direct anti-tumor action. The paradoxical recurrence-promoting finding of Pastore et al. [25] is the most difficult observation to reconcile; the dose-threshold design (≥20 mg/day for ≥2 years) may have selected patients with greater cardiovascular comorbidity and polypharmacy burden, who independently carry worse NMIBC prognosis [37]. The unique contributions of the present review include: the first synthesis specifically restricted to NMIBC; incorporation of the prospective Strobach cohort [18]; and identification of statin initiation timing relative to BCG as the most clinically important moderator identified to date. The broader context of drug repurposing in bladder cancer strengthens the biological plausibility: 5-alpha-reductase inhibitors have been associated with a 16–23% reduction in bladder cancer-specific mortality in a population-based Finnish cohort (post-diagnostic HR 0.77, 95% CI 0.68–0.88) [38] and GLP-1 receptor agonists were recently associated with significantly improved OS in propensity-matched bladder cancer cohorts (hazard ratio for non-use vs. use: 1.915, 95% CI 1.770–2.073) [39], underscoring that non-oncology pharmacological agents can meaningfully alter bladder cancer survival—a context within which statins merit continued and more rigorously designed investigation.

The current evidence base is insufficient to recommend statins as intentional oncologic adjuncts in NMIBC management, yet it does support two clinically actionable conclusions: (i) standard cardiovascular doses of statins do not impair BCG immunotherapy efficacy and need not be discontinued in NMIBC patients for whom they are independently indicated [20,21,23]; and (ii) patients who initiate statins prior to BCG may derive modest but measurable oncologic benefit, and awareness of this timing effect should inform future clinical and pharmacoepidemiological study designs. Given the high prevalence of dyslipidemia, hypertension, and cardiovascular disease in the predominantly elderly male NMIBC population [22], statins are co-prescribed in a substantial proportion of patients on independent grounds, and optimizing adherence to guideline-recommended cardiovascular pharmacotherapy may have dual clinical value. Poor glycemic control - independently associated with a 58% excess risk of bladder cancer-specific mortality in a population-based Finnish cohort [40] should be incorporated as a mandatory stratification variable in future statin trials to disentangle metabolic from statin-specific survival contributions. The highest research priority is a prospective RCT or biomarker-stratified cohort study specifying: a lipophilic statin agent (atorvastatin or simvastatin) at a standardized dose; initiation 4–8 weeks prior to BCG induction; NMIBC-specific eligibility restricted to intermediate- or high-risk disease; primary endpoint of 2-year RFS; and secondary endpoints including CSS, OS, BCG response rate, and mevalonate pathway biomarkers in tumor tissue and urine. A platform trial design co-evaluating statins alongside other repurposed agents—such as 5-alpha-reductase inhibitors [38] and GLP-1 receptor agonists [39] would maximize statistical efficiency in this population.

Several methodological limitations constrain the conclusions of this review and must be transparently acknowledged. First, all 11 included studies are observational, rendering causal inference impossible and exposing results to multiple systematic biases that disproportionately affect statin research: confounding by indication (statin users are healthier and more adherent to medical care), immortal-time bias (failure to correctly account for the period between NMIBC diagnosis and statin initiation or prescription dispensing), and the healthy user effect [41]. These biases collectively tend to inflate apparent statin benefit in observational data and cannot be eliminated by multivariable adjustment alone. Second, substantial clinical and methodological heterogeneity—across NMIBC stage and risk grade, BCG regimen and maintenance duration, statin type, dose definition, follow-up duration (24 months to 11.3 years), and outcome ascertainment—precluded formal meta-analysis; pooling effect estimates in this context would have been statistically inappropriate. Third, comorbidity burden constitutes a critical uncontrolled confounder: comorbidities are independently associated with substantially inferior survival in bladder cancer patients (3- and 5-year mortality more than 2-fold higher with CCI ≥3) [37], and the obesity paradox in bladder cancer—in which higher BMI paradoxically predicts better OS and CSS—illustrates the complex interplay of metabolic factors and oncologic outcomes [42]. Fourth, statin exposure was variably and imprecisely defined in most studies, relying on medical chart review without pharmacy claims or dispensing record verification, thereby precluding assessment of adherence, dose titration, or duration of continuous use. Fifth, three studies had small sample sizes (n=90–122) [19,21,23], conferring high risk of type II error for individual survival endpoints. Sixth, publication bias cannot be excluded, as null findings and negative associations may be underrepresented. Finally, restriction of the primary search to PubMed/MEDLINE, without supplementary searches of EMBASE or Cochrane, and the absence of PROSPERO pre-registration represent additional procedural limitations of the present review.

Conclusion

In a disease context where BCG immunotherapy—the most effective intravesical agent—fails in up to 40% of high-risk patients and no pharmacological adjunct has been established to improve long-term survival, identifying safe and biologically plausible co-administered agents is a genuine unmet clinical need. This first systematic review restricted exclusively to NMIBC, synthesizing 11 observational studies enrolling 29,370 patients, demonstrates that concomitant statin use is associated with a consistent and reproducible modest overall survival benefit—most robustly when initiated prior to intravesical BCG—without adversely affecting BCG immunotherapy efficacy. This oncologic safety profile, combined with the frequency of independent cardiovascular indications in the elderly NMIBC population, positions statins as a clinically relevant candidate for prospective investigation as an oncologic adjunct.

Cancer-specific survival, recurrence-free survival, and progression-free survival improvements were not consistently demonstrated across independent cohorts, and whether the observed OS benefit reflects a direct anti-tumor effect or a cardiovascular survival advantage remains unresolved; the identification of statin initiation timing relative to BCG as the most important moderator of effect represents the most clinically actionable finding of this review.

The primary constraint limiting definitive conclusions is that all 11 included studies are observational and subject to confounding by indication, immortal-time bias, and comorbidity confounding that cannot be eliminated by multivariable adjustment; substantial heterogeneity in statin classification, NMIBC risk stratification, BCG regimen, and follow-up duration further precludes quantitative synthesis. Statins should not be discontinued in NMIBC patients receiving BCG for whom they are independently indicated on cardiovascular grounds, and the pre-BCG timing signal warrants prospective validation before clinical translation. Future research should prioritize adequately powered randomized trials specifying a lipophilic statin agent at a standardized dose, initiated prior to BCG induction in intermediate- to high-risk NMIBC with pre-specified EAU risk-group stratification, glycemic status as a mandatory co-variable, and mechanistic biomarker endpoints—including mevalonate pathway activity and tumor immunophenotyping—to establish whether statins can be purposefully and safely incorporated into NMIBC management strategies.

Acknowledgements

The authors thank the PubMed/MEDLINE database for providing open access to the literature used in this review. No funding was received for this work.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, et al. (2024) Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74(3): 229-263.
2. Kung T-C, Jiang Y-H, Kuo H-C (2026) Prognostic factors for the recurrence, progression, and multiple recurrences of non-muscle-invasive bladder cancer in Eastern Taiwan. Tzu Chi Med J 38(1): 83-89.
3. Kim HS, Ku JH, Kim SJ, Hong SJ, Hong SH, et al. (2016) Prognostic Factors for Recurrence and Progression in Korean Non-Muscle-Invasive Bladder Cancer Patients: A Retrospective, Multi-Institutional Study. Yonsei Med J 57(4): 855-864.
4. Aydin YM, Mungan NA (2026) Early Recurrence Following Complete Initial Resection Predicts Adverse Oncological Outcomes in NMIBC. J Clin Med 15(6): 2463.
5. Bazarbashi SN, Azouz HJ, Abu Sabaa AH, Aljubran AH, Alzahrani AM, et al. (2016) Recurrence and progression in nonmuscle invasive transitional cell carcinoma of urinary bladder treated with intravesical Bacillus Calmette-Guerin: A single center experience and analysis of prognostic factors. Urol Ann 8(3): 333-337.
6. Slusarczyk A, Zapala P, Zapala L, Radziszewski P (2023) The impact of smoking on recurrence and progression of non-muscle invasive bladder cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol 149(6): 2673-2691.
7. Huang X, Liang N, Zhang F, Lin W, Ma W (2024) Lovastatin-Induced Mitochondrial Oxidative Stress Leads to the Release of mtDNA to Promote Apoptosis by Activating cGAS-STING Pathway in Human Colorectal Cancer Cells. Antioxidants 13(6): 679.
8. Khan S, Huda B, Bhurka F, Patnaik R, Banerjee Y (2025) Molecular and Immunomodulatory Mechanisms of Statins in Inflammation and Cancer Therapeutics with Emphasis on the NF-kappaB, NLRP3 Inflammasome, and Cytokine Regulatory Axes. Int J Mol Sci 26(17): 8429.
9. Santoni M, Monteiro FSM, Massari F, Abahssain H, Aurilio G, et al. (2022) Statins and renal cell carcinoma: Antitumor activity and influence on cancer risk and survival. Crit Rev Oncol Hematol 176: 103731.
10. El-Ashmawy NE, Khedr EG, El-Bahrawy HA, Al-Tantawy SM (2017) Chemopreventive effect of omega-3 polyunsaturated fatty acids and atorvastatin in rats with bladder cancer. Tumour Biol 39(2): 1010428317692254.
11. Yang J, Li C, Shen Y, Zhou H, Shao Y, et al. (2020) Impact of statin use on cancer-specific mortality and recurrence: A meta-analysis of 60 observational studies. Medicine 99(14): e19596.
12. Zhang X, Geng J, Zhang X, Peng B, Che J, et al. (2013) Statin use and risk of bladder cancer: a meta-analysis. Cancer Causes Control 24(4): 769-776.
13. Kuo C-C, Chiu H-F, Lee I-M, Kuo H-W, Lee C-T, et al. (2012) Statin use and the risk of bladder cancer: a population-based case-control study. Expert Opin Drug Saf 11(5): 733-738.
14. Richard PO, Ahmad AE, Bashir S, Hamilton RJ, Nam RK, et al. (2017) Effect of statins as a secondary chemopreventive agent among individuals with non-muscle-invasive bladder cancer: A population-based analysis. Urol Oncol 35(6): 342-348.
15. Liu K, Nicoletti R, Zhao H, Chen X, Chiu PK-F, et al. (2025) The potential benefits of concomitant statins treatment in patients with non-muscle-invasive bladder cancer. BJU Int 135(1): 88-94.
16. Crivelli JJ, Xylinas E, Kluth LA, da Silva RD, Chrystal J, et al. (2013) Effect of statin use on outcomes of non-muscle-invasive bladder cancer. BJU Int 112(2): E4-12.
17. Symvoulidis P, Tsioutis C, Zamboglou C, Agouridis AP (2023) The Effect of Statins on the Incidence and Prognosis of Bladder Cancer: A Systematic Review and Meta-Analysis. Curr Oncol 30(7): 6648-6665.
18. Strobach D, Haimerl L, Mannell H, Stief CG, Karl A, et al. (2023) The Characterization of Non-oncologic Chronic Drug Therapy in Bladder Cancer Patients and the Impact on Recurrence-Free and Cancer-Specific Survival: A Prospective Study. J Clin Med 12(21): 6749.
19. Wang Z, Ong WYF, Shen T, Sng J-H, Lata RM, et al. (2022) Beyond diabetes mellitus: role of metformin in non-muscle-invasive bladder cancer. Singapore Med J 63(4): 209-213.
20. Ndukwe E, Lotan P, Risk M, Koehne EL, Shapiro DD, et al. (2025) Statins Are Not Associated with Improved Bladder Cancer Outcomes in Patients with Early-Stage Bladder Cancer Treated with BCG Immunotherapy. Cancers 17(12): 2027.
21. Singla N, Haddad AQ, Passoni NM, Meissner M, Lotan Y (2017) Anti-inflammatory use may not negatively impact oncologic outcomes following intravesical BCG for high-grade non-muscle-invasive bladder cancer. World J Urol 35(1): 105-111.
22. Brooks NA, Kokorovic A, Xiao L, Matulay JT, Li R, et al. (2021) The obesity paradox: defining the impact of body mass index and diabetes mellitus for patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guerin. BJU Int 128(1): 65-71.
23. Skolarus TA, Lee EW, Virgo KS, Katz MD, Hudson MA, et al. (2009) Intravesical bacille Calmette-Guerin therapy for non-muscle-invasive bladder cancer: effects of concurrent statin therapy. J Am Coll Surg 209(2): 248-253.
24. Ferro M, Marchioni M, Lucarelli G, Vartolomei MD, Soria F, et al. (2021) Association of statin use and oncological outcomes in patients with first diagnosis of T1 high grade non-muscle invasive urothelial bladder

cancer: results from a multicenter study. Minerva Urol Nephrol 73(6): 796-802.

25. Pastore A, Palleschi G, Fuschi A, Silvestri L, Al Salhi Y, et al. (2015) Can daily intake of aspirin and/or statins influence the behavior of non-muscle invasive bladder cancer? A retrospective study on a cohort of patients undergoing transurethral bladder resection. BMC Cancer 15: 120.

26. Jia X, Lu Y, Xu Z, Mu Q (2023) Impact of statin use on breast cancer recurrence and mortality before and after diagnosis: a systematic review and meta-analysis. Front Oncol 13: 1256747.

27. McKechnie T, Brown Z, Lovrics O, Yang S, Kazi T, et al. (2024) Concurrent Use of Statins in Patients Undergoing Curative Intent Treatment for Triple Negative Breast Cancer: A Systematic Review and Meta-Analysis. Clin Breast Cancer 24(3): e103-e115.

28. Tsubaki M, Takeda T, Matsuda T, Kishimoto K, Takefuji H, et al. (2023) Statins enhances antitumor effect of oxaliplatin in KRAS-mutated colorectal cancer cells and inhibits oxaliplatin-induced neuropathy. Cancer Cell Int 23(1): 73.

29. Kamal A, Boerner J, Assad H, Chen W, Simon MS (2024) The Effect of Statins on Markers of Breast Cancer Proliferation and Apoptosis in Women with In Situ or Early-Stage Invasive Breast Cancer. Int J Mol Sci 25(17): 9587.

30. Tripathi S, Gupta E, Naik R, Khare S, Mir R, et al. (2025) Statins exhibit anti-tumor potential by modulating Wnt/beta-catenin signaling in colorectal cancer. Oncotarget 16:562-581.

31. Anger RM, Gobel A, Hofbauer LC, Rachner TD (2025) Rac1 inhibition promotes antitumor activity of statins in bone-seeking breast cancer cells. Biochem Biophys Res Commun 792: 152967.

32. Ishizuka Y, Satake Y, Kimura S, Yamashita S, Kawamorita N, et al. (2024) Statin administration ameliorates ischemia-induced overactive bladder with improvement of blood flow and anti-inflammatory effects in rats. Neurourol Urodyn 43(4): 991-1002.

33. Manthravadi S, Shrestha A, Madhusudhana S (2016) Impact of statin use on cancer recurrence and mortality in breast cancer: A systematic review and meta-analysis. Int J Cancer 139(6): 1281-1288.

34. Scott OW, Tin Tin S, Cavadino A, Elwood JM (2025) Statin use and breast cancer-specific mortality and recurrence: a systematic review and meta-analysis including the role of immortal time bias and tumour characteristics. Br J Cancer 133(4): 539-554.

35. Inasu M, Feldt M, Jernstrom H, Borgquist S, Harborg S (2022) Statin use and patterns of breast cancer recurrence in the Malmo Diet and Cancer Study. Breast 61: 123-128.

36. Mohsin S, Hasan M, Mustafa F, Kumar J, Aleissa M, et al. (2025) Impact of statin therapy on postoperative outcomes following colorectal cancer surgery: A systematic review. World J Gastrointest Surg 17(12): 112841.

37. Lund L, Jacobsen J, Clark P, Borre M, Norgaard M (2010) Impact of comorbidity on survival of invasive bladder cancer patients, 1996-2007: a Danish population-based cohort study. Urology 75(2): 393-398.

38. Makela VJ, Kotsar A, Tammela TLJ, Murtola TJ (2018) Bladder Cancer Survival of Men Receiving 5alpha-Reductase Inhibitors. J Urol 200(4): 743-748.

39. Kohler J, Buck L, Schliesser P, Weische O, Risch J, et al. (2026) Survival association of GLP-1 receptor agonists and SGLT2 inhibitors in bladder cancer patients. Urol Oncol 44(8): 92-100.

40. Vuoristo L, Poyhonen A, Vuorlaakso SM, Kotsar A, Tammela TLJ, et al. (2025) Hyperglycemia and bladder cancer prognosis in a Finnish population-based cohort. PLoS One 20(12): e0338215.

41. Emilsson L, Garcia-Albeniz X, Logan RW, Caniglia EC, Kalager M, et al. (2018) Examining Bias in Studies of Statin Treatment and Survival in Patients with Cancer. JAMA Oncol 4(1): 63-70.

42. Tseng W-H, Chiang T-Y, Ho C-H, Huang SK, Chiu AW, et al. (2024) Navigating the obesity paradox in bladder cancer prognosis-insights from the Taiwan National Health Insurance System Database. Front Nutr 11: 1433632.