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Gender-Specific Differences in Recurrence and Progression following Bacillus Calmette-Guérin Instillation for Non-Muscle-Invasive Bladder Cancer

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Keywords
Bladder cancer · Urothelial cancer · MIBC · BCG · Gender

Abstract

Introduction: To assess gender-specific differences in recurrence-free survival (RFS), progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS) among patients with intermediate or high-risk non-muscle-invasive bladder cancer (NMIBC) receiving BCG was the primary aim of this systematic review and meta-analysis. ***Methods:*** In July 2023, we performed a literature search using MEDLINE, Embase, and the Cochrane Library. This study was prospectively registered at PROSPERO (CRD 2023443269). The detailed review protocol is accessible via CRD. ***Results:*** The systematic literature search identified 6,723 studies, of which 38 fulfilled the inclusion criteria. Random-effect meta-analysis for RFS, based on data from 24 studies, revealed no statistically significant gender-specific difference (HR comparing males to females = 0.9618, 95% CI: 0.8408–1.1003, p = 0.5707). Similarly, for PFS, incorporating data from 14 studies, no statistically significant difference (HR = 0.9540, 95% CI: 0.7709–1.1805, p = 0.6648), for CSS, analysis of data from three studies yielded no statistically significant difference (HR = 0.9228, 95% CI: 0.6196–1.3743, p = 0.6925), and for OS, based on data from two studies, no statistically significant difference was observed (HR = 1.1436, 95% CI: 0.5092–2.5684, p = 0.7452). The risk of bias assessment indicated an overall moderate to high risk of bias. ***Conclusion:*** The findings indicate no association between gender and oncologic outcomes following BCG.

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Introduction

Following the 2018 GLOBOCAN data, urothelial carcinoma of the bladder is the 10th most common malignancy worldwide, with 549,393 new cases and 200,000 cancer-related deaths. In the USA, bladder cancer comprises 5% of new cancer diagnoses and is the sixth most prevalent malignancy. Approximately 75% of the newly diagnosed patients have non-muscle-invasive bladder cancer (tumor that spreads to the mucosa [carcinoma in situ, Ta] and lamina propria [stage T1]), while the remaining 25% of the patients have muscle-invasive carcinoma (tumor invasion to the muscle layer of the bladder; stage T2 and beyond). Prognosis depends on the type of bladder cancer, with 5-year rates ranging from 96% for non-muscle-invasive bladder cancer to 5% for metastatic cases. An estimated 17,240 deaths were caused by bladder cancer in the USA in 2018 [1, 2]. Nearly the same is reported in the most recent GLOBOCAN data of 2020 [3]. In the European Union, the age-standardized incidence rate is 20 in men and 4.6 in women. Worldwide, the bladder cancer age-standardized mortality rate (per 100,000 person/years) is 3.3 for men vs. 0.86 for women reported in 2021 [4].

Concerning the risk of recurrence and progression of the tumor non-muscle-invasive bladder cancer (NMIBC) is stratified into four different risk groups by the European Association of Urology (EAU). As an example, the very high-risk group is defined as follows: Ta high risk (HG)/G3 and CIS with all three risk factors (age >70, multiple papillary tumors, tumor diameter ≥3 cm), T1G2 and CIS with at least 2 risk factors, T1 HG/G3 and CIS with at least 1 risk factor and T1 HG/G3 no CIS with all 3 risk factors. Interestingly, the probability for progression in this very high-risk group in 10 years is about 59% (95% CI: 39%–79%) and for the high-risk-group it is 14% (CI: 10%–19%). For these reasons, these patients require a life-long follow-up and that is also why NMIBC is considered one of the most cost-intensive malignancies worldwide [4].

However, the systematic review will focus on intermediate and high-risk NMIBC patients since these patients should receive Bacillus Calmette-Guérin (BCG) instillation immunotherapy following transurethral resection of the bladder tumor (TUR-BT) to reduce the risk of tumor recurrence as well as progression to muscle-invasion according to the EAU guideline [4]. Furthermore, there are hints from trials and literature that there are significant differences in therapy response to BCG between men and women in urothelial bladder cancer. Unfortunately, the data are still inconclusive, and a very detailed reflection is necessary [3–5]. However, this detailed reflection has the potential to individualized medicine and further improvement of outcomes.

Consequently, the primary aim of this systematic review and meta-analysis was to evaluate gender-specific differences in recurrence-free survival (RFS), progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS) in patients with intermediate and high-risk NMIBC receiving BCG adjuvant instillation. The secondary aims were gender-specific differences in adverse events and quality of life (QoL).

Methods

Search Strategy

In July 2023, we performed a systematic literature search using MEDLINE via PubMed, Embase, and the Cochrane Library. The search algorithm broadly included the search term clusters gender, bladder cancer, NMIBC, outcomes and BCG. The online supplementary File 1 (for all online suppl. material, see https://doi.org/10.1159/000542473) details the complete search algorithms. Reference lists of included articles, as well as review articles, were searched to identify additional records. No restrictions were made concerning language, study region, or publication type. Publication date was included after January 1976 because BCG therapy was first introduced for NMIBC by then. This study was prospectively registered at PROSPERO (https://www.crd.york.ac.uk/prospero/; ID CRD 2023443269).

Study Inclusion and Exclusion Criteria

The predefined primary outcomes were gender-specific differences in RFS, PFS, CSS and OS following single intravesical instillation therapy with BCG in intermediate- and high-risk NMIBC. We included randomized controlled trials (RCTs) as well as prospective clinical trial (non-RCTs) and retrospective cohort studies. Combination therapies with radiotherapy, chemotherapy or other targeted therapies were excluded. Furthermore, patients with a history of prior intravesical therapies within 6 months preceding BCG initiation were excluded to minimize potential confounding effects. The larger and more comprehensive publication was included if more than one publication evaluated the same patient cohort.

Data Extraction

An a priori defined standardized data extraction process was used for every included record. Extracted variables included author(s), year of publication, study

country, population size, percentage of female patients, cancer stage and grade, histopathological cancer subtype, length of follow-up, details on BCG as well as dosing in the included studies, variables adjusted for in multivariable Cox regression models and HR or OR measures with the associated 95% CI for RFS, PFS, CSS and OS. Study extraction was independently performed by two review authors. Inconsistencies were resolved by a third review author. The online platform covidence (https://www.covidence.org/; Veritas Health Innovation Ltd, Melbourne, Australia) was used for the screening and data extraction process.

Study Quality Assessment

Two reviewers independently assessed the risk of bias with the ROBINS-I-tool or the Cochrane Risk of Bias tool RoB2 as appropriate [6]. The ROBINS-I tool includes seven domains of bias: risk of bias due to confounding, bias in the selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes and bias in the selection of the reported results for one outcome measurement. The domains are combined to an overall risk of bias. The RoB2 tool summarizes five risk of bias domains: bias arising from randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported results. These domains are also combined to an overall risk of bias. Any disagreements were resolved by the involvement of a third review author.

Statistical Analysis

Comparison of gender-specific differences in survival parameters was performed using the inverse variance method weighting for pooling of continuous outcome data to account for clinical heterogeneity [7]. In all provided analyses, male patients were considered the referent. Studies providing estimates with a female referent were back-calculated by inversing the hazard ratios (HR) and the associated confidence intervals (CIs). Between studies, heterogeneity was assessed by the I^2 statistic with the associated 95% CI, the chi-square p values of heterogeneity and visual inspection of forest plots. Heterogeneity was interpreted as limited – I^2 = 0–40%, moderate – I^2 = 41–60%, substantial – I^2 = 61–80%, and considerable I^2 = 81–100%. Subgroup analyses were conducted to identify potential sources of heterogeneity. Subgroups were chosen a priori and included analysis by year, only receiving induction therapy, patients receiving induction and maintenance, patients only receiving primary TUR-BT, inclusion of more than 20% patients with recurrent NMIBC, patient with a median age over and under 70 years patients, only uni- or multivariate assessment and study region. In addition, change of pooled HR over the years of publication was assessed. Publication bias was assessed by visual inspection of the funnel plot and by Egger's test. All statistical analyses were performed with *R* version 4.2.1 (https://www.r-project.org/) and RStudio (RStudio, Boston, MA) and the *R* package meta [8]. The alpha level indicating statistical significance was predefined as 0.05 for all analyses except the assessment of heterogeneity, which was considered at alpha = 0.1. All provided p values are 2-sided.

Results

Study Characteristics

The systematic literature search identified 6,723 studies of which 38 fulfilled the inclusion criteria. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart is shown in Figure 1. The characteristics of the included studies are summarized in Table 1.

All studies were published in English language between the years 1989 and 2023 and included only patients with urothelial cancer and only receiving BCG intravesical. Five studies (13%) were available only as conference abstracts. Fourteen studies were designed in a multicenter setting and only two were randomized controlled studies whereas the remainders were cohort studies. Seven studies had a prospective setting. The study regions included North America, Europe, and Asia.

In six studies the evaluation of gender-specific differences was part of the study's aim. Furthermore, 25 studies (66%) used multivariate models with gender as covariate. The study size ranged from 45 to 3,035 patients and included 8.9–35.7% female participants (available for 33 studies, 87%). Median/mean patient age ranged from 62 to 74 years (available for 18 studies, 47%). At the time of treatment six studies included more that 20% of patients who already had a relapse (data available for 15 studies, 39%). The BCG strains used were mostly Connaught, Tokyo, and TICE (information available for 28 studies 74%). In 14 studies (37%) the patients received induction therapy only.

The outcomes evaluated were RFS (29 studies), PFS (25 studies), OS (5 studies), adverse events (5 studies, but no gender-specific differences reported), and others (14 studies). The length of follow-up, if documented ranged from 25 to 102 months (available for 33 studies, 87%). Pooling was possible for the outcomes RFS, PFS, CSS, and OS.

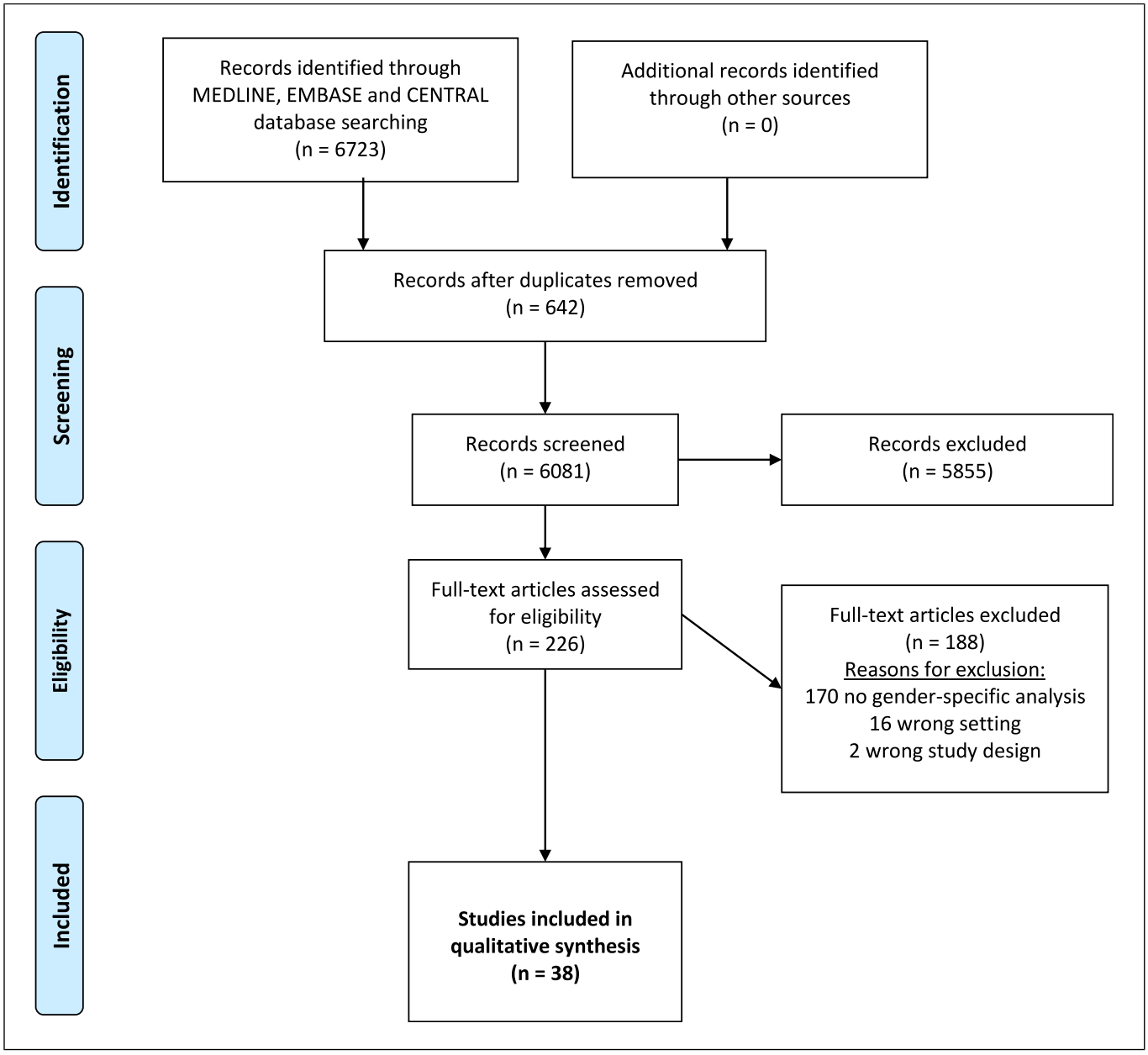

Fig. 1. Prisma flowchart.

Pooled Analysis for RFS

Random-effect meta-analysis for RFS included data from 24 studies and yielded no statistically significant gender-specific difference (HR comparing males to females = 0.9618, 95% CI: 0.8408–1.1003, $p = 0.5707$). Figure 2 shows the forest plot of the random-effect meta-analysis. Heterogeneity was moderate ($I^2 = 47.0\%$; $p = 0.0062$). No publication bias was detected upon visual inspection (online suppl. File 2) and statistical testing (Egger's test $p = 0.8735$).

Pooled Analysis for PFS

Random-effect meta-analysis for PFS included data from 14 studies and yielded no statistically significant gender-specific difference (HR = 0.9540, 95% CI: 0.7709–1.1805, $p = 0.6648$). Figure 3 shows the forest plot of the random-effect meta-analysis. Heterogeneity was moderate ($I^2 = 56.8\%$; $p = 0.0046$). No publication bias was detected upon visual inspection (online suppl. File 2) and statistical testing (Egger's test $p = 0.7052$).

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Table 1. Summary of study characteristics (n = 38)

Reference	Study design	Participants, *n*	Percentage of females	Evaluation of gender-specific differences as study aim	BCG strain used	Induction/ maintenance	Outcomes	Median length of follow-up, months
Ajili et al. [9] (2013)	Cohort retrospective, monocentric	45	8.9	No	Pasteur	Induction and maintenance	RFS; PFS	30.0
Andius et al. [10] (2004)	Cohort prospective, monocentric	236	30.5	No	Danish, TICE	Induction and maintenance	RFS; PFS	44.0
Barry et al. [11] (2021)	Cohort retrospective, monocentric	149	24.8	No	N/A	Induction and maintenance	PFS; other	32.9 (mean)
Birkhauser et al. [12] (2012)	Randomized controlled trial, multicentric	149	N/A	No	Connaught, TICE	Induction and maintenance	RFS; PFS; other	25.0
Boorjian et al. [13] (2010)	Cohort retrospective, monocentric	1,021	25.9	Yes	Connaught	Induction only	RFS; PFS; other	36
Bree et al. [14] (2021)	Cohort retrospective, monocentric	541	20.5	Yes	N/A	Induction and maintenance	RFS; PFS; OS	45.2
Chen et al. (2022) [15]	Cohort retrospective, monocentric	160	20.0	No	TICE, Connaught	Induction and maintenance	RFS; PFS; adverse events	32.0
D'Andrea et al. [16] (2020)	Cohort retrospective, multicentric	660	19.2	No	Moreau, TICE	Induction and maintenance	RFS; PFS	41.0
D'Andrea et al. [17] (2021)	Cohort retrospective, multicentric	2,635	18.0	Yes	N/A	Induction and maintenance	Other	50.0
Decobert et al. [18] (2008)	Cohort prospective, multicentric	111	18.0	No	N/A	Induction and maintenance	RFS; other	31.0
Fadel et al. [5] (2022)	Cohort retrospective, monocentric	613	23.0	Yes	N/A	Induction and maintenance	Other	N/A
Gontero et al. [19] (2015)	Cohort retrospective, multicentric	2,451	17.9	No	N/A	Induction and maintenance	RFS; PFS; OS; other	61.0

Table 1 (continued)

Reference	Study design	Participants, *n*	Percentage of females	Evaluation of gender-specific differences as study aim	BCG strain used	Induction/ maintenance	Outcomes	Median length of follow-up, months
Herr et al. [20] (1989)	Cohort retrospective, monocentric	221	N/A	No	Pasteur	Induction and maintenance	OS; other	60.0
Herr et al. [21] (2007)	Cohort retrospective, monocentric	805	23.4	No	Connaught	Induction only	RFS; PFS; other	24.0 (minimum)
Hurle et al. [22] (2018)	Cohort prospective, monocentric	185	22.7	No	TICE	Induction and maintenance	RFS; PFS; other	93.0
Iida et al. [23] (2016)	Cohort retrospective, multicentric	207	22.7	No	Tokyo	Induction only	RFS	33.5
Irie et al. [24] (2003)	Cohort prospective, monocentric	80	15.0	No	Tokyo	Induction only	RFS	27.5
Kakiashvili et al. [25] (2011)	Cohort retrospective, multicentric	136	18.4	No	N/A	Induction only	RFS; PFS; OS	78.0 (mean)
Kamat et al. [26] (1994)	Cohort prospective, monocentric	95	12.6	No	Danish 1,331	Induction only	RFS; PFS; other	32.0 (mean)
Kikuchi et al. [27] (2022)	Cohort retrospective, monocentric	146	25.3	No	Tokyo 172, Connaught	Induction only	RFS; PFS	61.0
Kim et al. [28] (2018)	Cohort retrospective, monocentric	64	10.9	No	Connaught, TICE	Induction only	RFS; PFS	N/A
Koguchi et al. [29] (2020)	Cohort retrospective, monocentric	78	21.8	No	Tokyo	Induction and maintenance	RFS; adverse events	36.2
Krajewski et al. [30] (2020)	Cohort retrospective, multicentric	637	16.3	No	TICE, RIVM, Moreau, Connaught	Induction and maintenance	RFS; PFS; other	57.0
Liu et al. [31] (2023)	Cohort retrospective, multicentric	2,602	N/A	No	Connaught, Tokyo, Danish	Induction and maintenance	RFS; PFS; OS; other	N/A
Milosevic et al. [32] (2014)	Cohort retrospective, monocentric	899	N/A	Yes	N/A	Induction and maintenance	Other	N/A

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Table 1 (continued)

Reference	Study design	Participants, *n*	Percentage of females	Evaluation of gender-specific differences as study aim	BCG strain used	Induction/ maintenance	Outcomes	Median length of follow-up, months
Miyamoto et al. [33] (2021)	Cohort retrospective, monocentric	165	13.3	No	Tokyo, Connaught	Induction only	RFS; PFS	53.0
Montesino-Semper et al. [34] (2010)	Cohort retrospective, multicentric	138	N/A	No	Connaught	Induction and maintenance	RFS; PFS	62.5
Muto et al. [35] (2013)	Cohort retrospective, monocentric	104	13.5	No	Connaught	Induction and maintenance	RFS; PFS	induction group: 42.3 (mean), maintenance group 51.1 (mean)
Nurminen et al. [36] (2023)	Cohort retrospective, multicentric	723	16.0	No	RIVM, TICE	Induction and maintenance	RFS; PFS; adverse events; other	66.0
Okamura et al. [37] (2012)	Cohort retrospective, monocentric	75	12.0	No	Tokyo 172	Induction and maintenance	RFS; PFS; adverse events	102.0
Palou et al. [38] (2012)	Cohort retrospective, monocentric	146	12.3	Yes	Connaught	Induction only	RFS; PFS; OS; other	102.0
Shakhssalim et al. [39] (2023)	Randomized controlled trial prospective, monocentric	84	35.7	No	N/A	Induction and maintenance	RFS; PFS; adverse events	N/A
Shinka et al. [40] (1998)	Cohort retrospective, monocentric	141	17.7	No	Tokyo	Induction only	RFS; PFS	42.0 (mean)
Takashi et al. [41] (2002)	Cohort retrospective, multicentric	146	21.9	No	Tokyo 172	Induction only	RFS; PFS; OS	64.7
Tomida et al. [42] (2022)	Cohort retrospective, multicentric, multicentric	3,035	17.9	No	Tokyo, Connaught	Induction and maintenance	RFS; PFS	44.4
Williams et al. [43] (2021)	Cohort retrospective, multicentric	412	18.7	No	N/A	Induction and maintenance	RFS; PFS; other	70.5

Table 1 (continued)

Reference	Study design	Participants, *n*	Percentage of females	Evaluation of gender-specific differences as study aim	BCG strain used	Induction/ maintenance	Outcomes	Median length of follow-up, months
Yoneyama et al. [44] (2008)	Cohort retrospective, monocentric	150	24.7	No	Tokyo 172	Induction only	RFS; PFS; adverse events	40 mg group: 42.2, 80 mg group: 90.7
Yuge et al. [45] (2011)	Cohort retrospective, monocentric	447	17.7	No	Tokyo 172	Induction only	RFS; PFS; adverse events	51.0

Pooled Analysis for CSS

Random-effect meta-analysis for CSS included data from three studies and yielded no statistically significant gender-specific difference (HR = 0.9228, 95% CI: 0.6196–1.3743, $p = 0.6925$). Figure 4 shows the forest plot of the random-effect meta-analysis. Heterogeneity was moderate ($I^2 = 54.1\%$; $p = 0.1129$). We performed no analyses for publication bias due to low study number.

Pooled Analysis for OS

Random-effect meta-analysis for OS included data from 2 studies and yielded no statistically significant gender-specific difference (HR = 1.1436, 95% CI: 0.5092–2.5684, $p = 0.7452$). Supplementary 3 shows the forest plot of the random-effect meta-analysis. Heterogeneity was substantial ($I^2 = 61.7\%$; $p = 0.1063$). We performed no analyses for publication bias due to low study number.

Subgroup Analysis

Subgroup analyses were performed for the BCG scheme (only induction vs. induction and maintenance) for RFS and PFS and yielded no statistically significant gender-specific differences. Furthermore, analyses stratifying by study region, e.g., only Asian studies, for RFS and PFS yielded no significant gender-specific differences. We also performed analyses for studies which included gender as a covariate in a univariate vs. multivariate model for RFS and PFS: No significant gender-specific differences were evident. Similarly, analyses for RFS only including studies with primary but no secondary TUR-BT yielded no significant gender-specific differences. Finally, no statistically significant gender-specific differences were evident for RFS and PFS upon subgroup analyses including only studies with more than 20% relapse patients or only patients with median/mean age </>70 years.

Sensitivity Analysis

Sensitivity analyses for publication year were performed for RFS, PFS, CSS, and OS. No relevant changes in HR over the years were evident.

Secondary Study Aims

None of the included studies reported data about gender-specific differences in adverse events and quality of life (QoL).

Quality Assessment

The risk of bias assessment yielded an overall moderate to high risk of bias. Reasons for limited quality or serious risk of bias are mostly due to the retrospective study

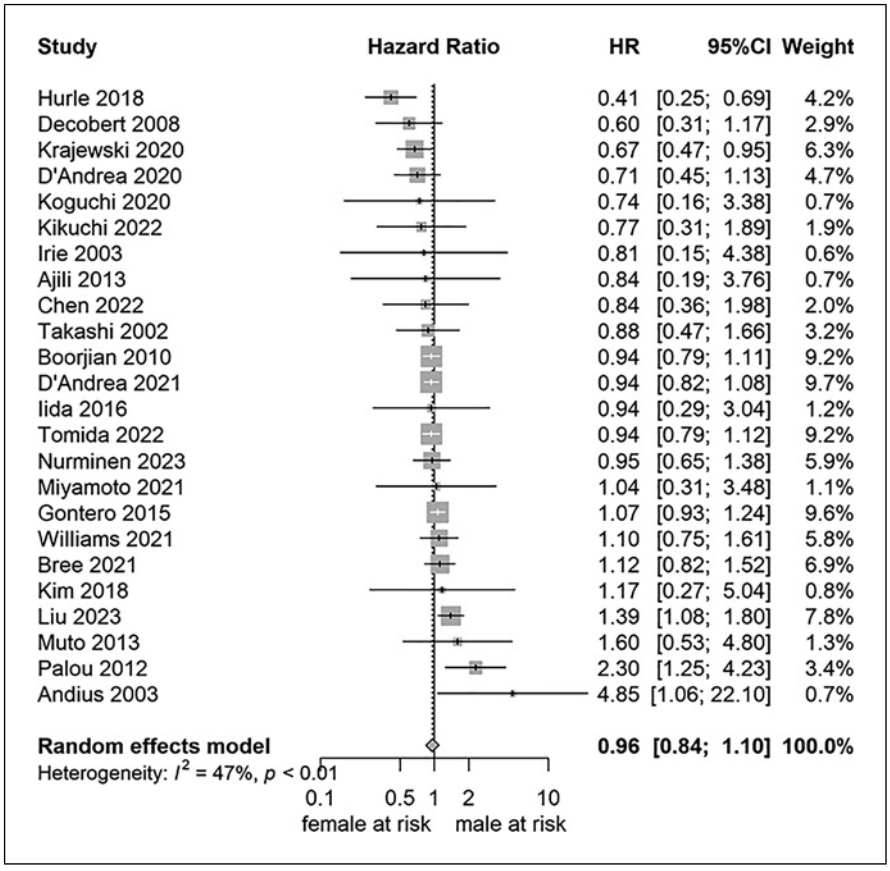

Fig. 2. Forest plot of the random-effect meta-analysis for RFS.

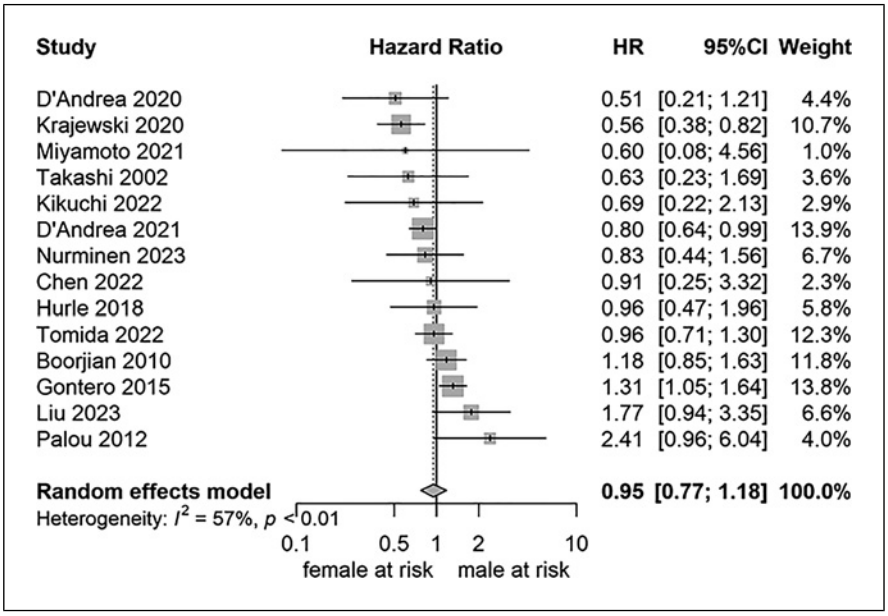

Fig. 3. Forest plot of the random-effect meta-analysis for PFS.

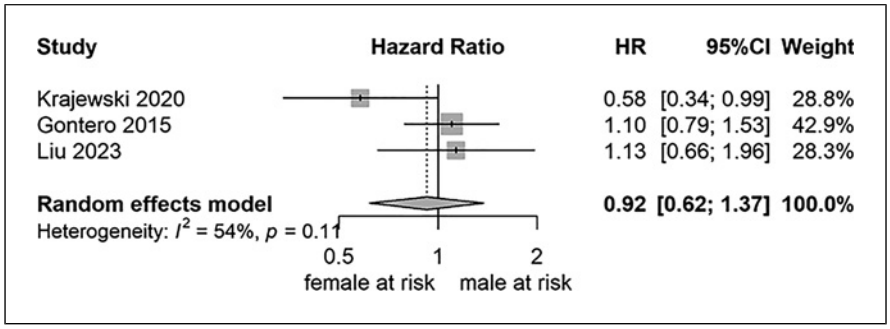

Fig. 4. Forest plot of the random-effect meta-analysis for CSS.

designs or due to the fact that the results are published as conference abstracts. Online supplementary File 4 shows the detailed risk of bias assessment of the included studies.

Discussion

Our study reports the results from a systematic review and meta-analysis about gender-specific differences in BCG therapy for NMIBC. We found that the effect of BCG therapy is probably not gender-specific. The advantage of our meta-analysis is that we included only urothelial-differentiated cancer and only primary BCG administration intravesical. Furthermore, we excluded patients who received prior intravesical therapies, like cytostatic drugs, or there should have been at least 6 months between these different therapies; we excluded medication with other immune modulating drugs for NMIBC therapy, combination therapies, application aids and we did not consider BCG shortage for evaluation. Thereof, we generated a homogeneous cohort of NMIBC patients with BCG therapy for our meta-analysis.

Otherwise, gender-specific differences in response to intravesical BCG are still controversially discussed, but Bilski et al. [4] concluded in their recent very comprehensive retrospective study, that sex-specific discrepancies in outcomes of bladder cancer seem to be multifactorial, comprising molecular, physiological and anatomic features, heterogenous exposure and responses to carcinogens, as well as treatment-depend factors. Additionally, Fadel et al. [5] recently concluded that there is no clear evidence for sex-based differences in response to BCG treatment in regard to progression, recurrence, and tolerability. In summary, for gender-specific evaluations and individual therapy approaches you have to be very precise and look deep into details to identify possible confounders. Therefore, we also applied several subgroup analyses, if possible, which also revealed no gender-specific differences.

Our study is not devoid of limitations of which the majority can be attributed to the design as well as the risk of bias of the included studies. For example, the low percentages of female patients leave statistical tests with low power. Yet, for RFS and PFS a considerable number of studies could have been pooled. For almost all studies, the duration of the maintenance therapy, if applied, was not available. Similarly, the vesical retention time of the BCG-agent was not provided. These circumstances did not allow for further subgroup analyses. In addition, the mean/median patient age was not provided for the majority of the studies what limited the informative value of the subgroup analyses. The subgroup analyses were also limited by the low number of studies for the outcomes CSS and OS. No further subgroup analyses and no evaluation of publication bias were possible. Yet, these outcomes are less important for patients undergoing BCG therapy for NMIBC and may therefore play a minor role. Additionally, the included studies were very heterogenous in terms of the used risk classification of NMIBC, e.g., according to the EAU or AUA guideline, so we were not able to perform a subgroup analysis regarding this issue, despite their significant impact on oncologic outcomes as mentioned in the introduction. Unfortunately, there were no gender-specific about adverse events or QoL reported in the included studies. These are important points for therapy selection as well, and additionally adverse events can lead to termination of the instillation and so this might trigger worse outcome. In our opinion, further studies should also address this issue.

Concerning, the study quality there was an overall moderate to high risk of bias, mainly due to the retrospective study designs, but there were also other problems with reporting bias, e.g., information about duration of maintenance therapy (like discussed above) was not available. However, these data are important, like we also discussed above, for detailed reflection and

individualized, gender-specific, therapy approaches. Consequently, further studies should be really precise about therapy description and patient cohorts including risk classification.

Nevertheless, our meta-analysis is the first to thoroughly evaluate the gender-specific differences among patients receiving BCG instillation therapy for NMIBC. It provides the urologic community with a robust statement that there are probably no relevant gender-specific differences and that the known poorer outcomes for females with bladder cancer must be searched elsewhere, e.g., in instillation therapies using cytostatic intravesical chemotherapy. As an example: The data are in contrast to our recent meta-analysis, were we concluded that women are at increased risk for disease recurrence after local treatment of NMIBC compared with male patients. Reduced effectiveness of BCG treatment might underlie this observation. Gender-specific differences were evident across various subgroups and proved robust upon sensitivity analyses [46], but this meta-analysis also included patients with mixed therapeutic regimens (BCG and cytostatic intravesical chemotherapy), e.g., the study performed by Hara et al. [47] or the evaluation by Jancke et al. [48]. Therefore, cytostatic intravesical chemotherapy and its combinations might be potential drivers for gender-specific differences. Furthermore, we must suggest the hypothesis that women might be offered first BCG for NMIBC and respond worse than men to cytostatic intravesical chemotherapy, which is a present important topic, especially in the context of BCG shortage [49]. Consequently, our group registered and started a new systematic review and meta-analysis "Gender-specific differences in recurrence and progression following cytostatic intravesical chemotherapy for non-muscle-invasive bladder cancer (NMIBC)" (https://www.crd.york.ac.uk/prospero/; ID CRD 42024507059). However, it would be also of interest in this context to evaluate gender-specific differences in outcomes patients who failed BCG instillation and therefore underwent radical cystectomy.

In summary, our findings indicate no association between gender and oncologic outcomes following BCG therapy. Still, it is well reported that women have poorer outcomes in bladder cancer than men, so the drivers of this fact must be searched elsewhere, e.g., in instillation therapies using cytostatic intravesical chemotherapy in NMIBC.

Acknowledgments

The authors would like to thank Dr. Julia Lackner from UroEvidence from the German Society of Urology (DGU) for her guidance in the development of search strategies and validation of search strategies.

Statement of Ethics

A statement of ethics is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

All authors declare that they have no conflict of interest regarding this work.

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Author Contributions

L.S., B.K., and A.U.: conception, data validation, analysis, and supervision. L.S., B.K. J.K., F.Z., A.B., S.G., A.G., and A.U.: data extraction, quality assessment, critical review of the data, writing, and reviewing the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to ethical regulations in our institution but are available from the corresponding author (L.S.) upon reasonable request.

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