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REVIEW

A Systematic Literature Review of Real-World Treatment Effectiveness and Economic and Humanistic Burden in Patients With Muscle-Invasive Bladder Cancer Who Underwent Radical Cystectomy

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Purpose: Treatment options for muscle-invasive bladder cancer (MIBC) are generally limited to radical cystectomy (RC) with or without neoadjuvant chemotherapy (NAC), adjuvant chemotherapy (AC), or immunotherapy. To contextualize emerging data on novel therapies, a systematic literature review (SLR) was conducted to evaluate real-world treatment effectiveness and economic and humanistic burden in patients with MIBC who received RC with or without systemic therapy.

Methods: Literature searches identified studies (published January 2018–June 2023) in adult patients with MIBC who received RC in the US, Germany, France, Italy, Spain, and the UK and reported effectiveness, economic burden, or humanistic burden.

Results: Of 4192 references identified, 61 reported real-world effectiveness, 12 economic burden, and 5 humanistic burden. No studies on immunotherapy were identified. Reported median overall survival (OS) ranged from 0.7 to 8.3 years with RC alone (n=9), 1.8–7.5 years with NAC+RC (n=6), and 1.5–6.1 years with RC+AC (n=7). Hospital stays for RC had median length of 5–10 days (n=5) and cost >$34,000 in the US. Health-related quality of life (HRQOL) was reported during 1 to 2 years post RC (n=5), but approximately 40% of patients continued to experience high psychosocial distress or low HRQOL.

Conclusion: Real-world studies have reported modestly longer survival with NAC or AC over RC alone; however, rates of disease recurrence were high and OS remained poor. Given this and the high economic burden for patients with MIBC, more effective therapies are needed.

Keywords: adjuvant chemotherapy, muscle-invasive bladder cancer, neoadjuvant chemotherapy, radical cystectomy, systematic literature review

Introduction

Muscle-invasive bladder cancer (MIBC) accounts for approximately 30% of bladder cancer cases in the US.[1,2] The disease has a poor prognosis, with half of patients with MIBC subsequently developing metastases within 5 years.[3] The standard treatment for patients with MIBC, recommended by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines, is radical cystectomy (RC).[4,5] For patients who are eligible for cisplatin (around 50% of patients with MIBC[6]), cisplatin-based neoadjuvant chemotherapy (NAC) is recommended prior to RC.[4,7] NAC+RC has been shown to improve survival for patients with MIBC, with a meta-analysis of 11 clinical trials reporting an improvement in overall survival (OS) at 5 years from 45% with RC alone to 50% with NAC+RC.[8] Additionally, adjuvant cisplatin-based chemotherapy (AC) may be considered for cisplatin-eligible patients with high-risk pathology after RC where NAC was not used.[4,7,9] A meta-analysis of nine clinical trials

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suggested a survival benefit associated with treatment with AC; however, no survival benefit has so far been demonstrated in Phase III trials.[4,10] A more recent addition to the treatment landscape for MIBC is adjuvant immunotherapy with nivolumab, which may be considered for cisplatin-eligible or -ineligible patients with high-risk pathology after RC (ie, if cisplatin-based NAC was given and the tumor was staged as ypT2-ypT4a or ypN+, or if cisplatin-based NAC was not given and the tumor was staged as pT3, pT4, or pN+).[5] Adjuvant nivolumab was shown to improve disease-free survival (primary endpoint) in the CheckMate 274 trial (20.8 months [95% CI; 16.5–27.6] with nivolumab vs 10.8 months [95% CI, 8.3–13.9] with placebo; hazard ratio [HR] for disease recurrence or death 0.71 [98.22% CI, 0.58–0.86]),[11] but OS from the interim analyses has not yet reached statistical significance (median OS 69.5 [95% CI, 58.1–not evaluable] months for nivolumab and 50.1 [38.2– not evaluable] months and placebo; HR 0.76 [0.61–0.96]).[12]

Despite these available treatments, prior real-world studies indicate that utilization (<40%) of NAC and AC is relatively low in patients with MIBC.[13–15] A major reason for this is that only around 50% of patients with MIBC are cisplatin-eligible and subsequently eligible for NAC or AC. Ineligibility for cisplatin is particularly associated with older age (the median age of patients with MIBC is >70 years), and determined by factors including low renal function and hearing loss.[16] Other potential reasons for low utilization of systemic therapies even among eligible patients include socioeconomic factors such as income, insurance status, or distance to treatment facility.[13–15] As a more recent adjuvant treatment option for high-risk patients after RC, no real-world data are yet available on utilization of nivolumab in practice.

Given the low utilization of NAC or AC,[13–15] modest absolute survival benefit with NAC, and the limited availability of systemic therapies for cis-ineligible patients, there is a need for new systemic treatment options in MIBC. Several clinical trials that are currently ongoing or have recently disclosed data are investigating new therapies and approaches that might address this need.[17–22] In order to contextualize outcomes from new clinical trials, and to better characterize unmet need among patients with MIBC, there is a need to better understand the real-world effectiveness of currently available treatments, together with burden of disease, in patients with MIBC. To this end, a systematic literature review (SLR) was conducted to evaluate real-world treatment effectiveness and economic and humanistic burden in patients with MIBC who received RC with or without neoadjuvant or adjuvant systemic therapy.

Methods

The SLR was conducted in accordance with guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the National Institute for Clinical Excellence (NICE) Decision Support Unit guidance for evidence synthesis and decision-making.[23,24]

Literature searches in the EMBASE, Medline, PsycInfo, Econlit, and Cochrane Library electronic databases identified real-world studies (published between January 2018 and June 2023) of adult patients with MIBC who received or were scheduled for RC in France, Germany, Italy, Spain, the UK and the US, based on the criteria in Table 1. Searches were conducted on June 19, 2023. Additionally, a manual search of the reference lists of recent (January 2018–June 2023) and relevant SLRs and targeted literature reviews identified from the database searches was performed to ensure retrieval of any relevant publications not otherwise captured.

Title/abstract and full-text screening were conducted by two independent investigators with any disagreements resolved by discussion with a third investigator. Abstracts and full-text publications were screened for those reporting real-world effectiveness (including OS, progression-free survival [PFS], recurrence-free survival [RFS], metastasis-free survival [MFS], and time to cystectomy), economic burden, and humanistic burden (the impact on patients' wellbeing) (Table 1). Studies on patients who underwent bladder-sparing treatment or studies in which the treatment was unclear were excluded. Relevant data from the final selection of full-text publications were extracted into a tailored data extraction form. For each included study, data were extracted by a single investigator and independently validated by a second investigator. Any discrepancies were resolved by discussion between investigators, including a third more senior researcher, if needed.

Table 1 Study Eligibility Criteria

Category	Inclusion Criteria
Population	Adult patients with MIBC treated with or scheduled for RC
Geographic location	UK, Germany, France, Italy, Spain, and US
Sample size	N>100
Study designs	• Observational studies • Retrospective studies • Registry studies • Economic evaluations • Utility studies • Systematic and targeted reviews

Study outcomes	• Economic burden
	  ○ Direct costs
	  ○ Indirect costs
	  ○ Absenteeism/presenteeism
	  ○ Nonmedical costs associated with MIBC
	• Humanistic burden
	  ○ HRQOL outcomes
	  ○ Utility values
	  ○ Burden on family/caregiver
	• Real-world evidence
	  ○ Treatment patterns
	  ○ Real-world effectiveness of MIBC treatments
	  ○ OS
	  ○ Pathological complete response
	  ○ Pathological downstaging
	  ○ Duration of treatment
	  ○ Disease-free survival
	  ○ Event-free survival
	  ○ PFS
	  ○ RFS
	  ○ MFS
	  ○ Time to cystectomy

Language	English
Date of publication	January 2018–June 2023

Abbreviations: HRQOL, health-related quality of life; MFS, metastasis-free survival; MIBC, muscle-invasive bladder cancer; OS, overall survival; PFS, progression-free survival; RC, radical cystectomy; RFS, recurrence free survival.

Results

Study Selection

Of 4192 references identified, 76 were included following screening (Figure 1). Of these, 61 reported on effectiveness, 12 on economic burden, 5 on humanistic burden, and 1 on treatment guidelines. The majority (n=53) were from the US, 18 were from Europe (Germany, France, Italy, Spain, UK), and 5 were multinational. For both real-world effectiveness and economic burden studies, the majority of publications were from the US (46/61 and 9/12, respectively), whereas most humanistic burden studies were conducted in Germany (4/5). Forty-four studies reported on NAC before RC, 21 on RC+AC, and 30 on RC alone, with several studies reporting on more than one of these treatment types. No studies reported on patients who received perioperative chemotherapy (both NAC and AC) or on patients who received immunotherapy.

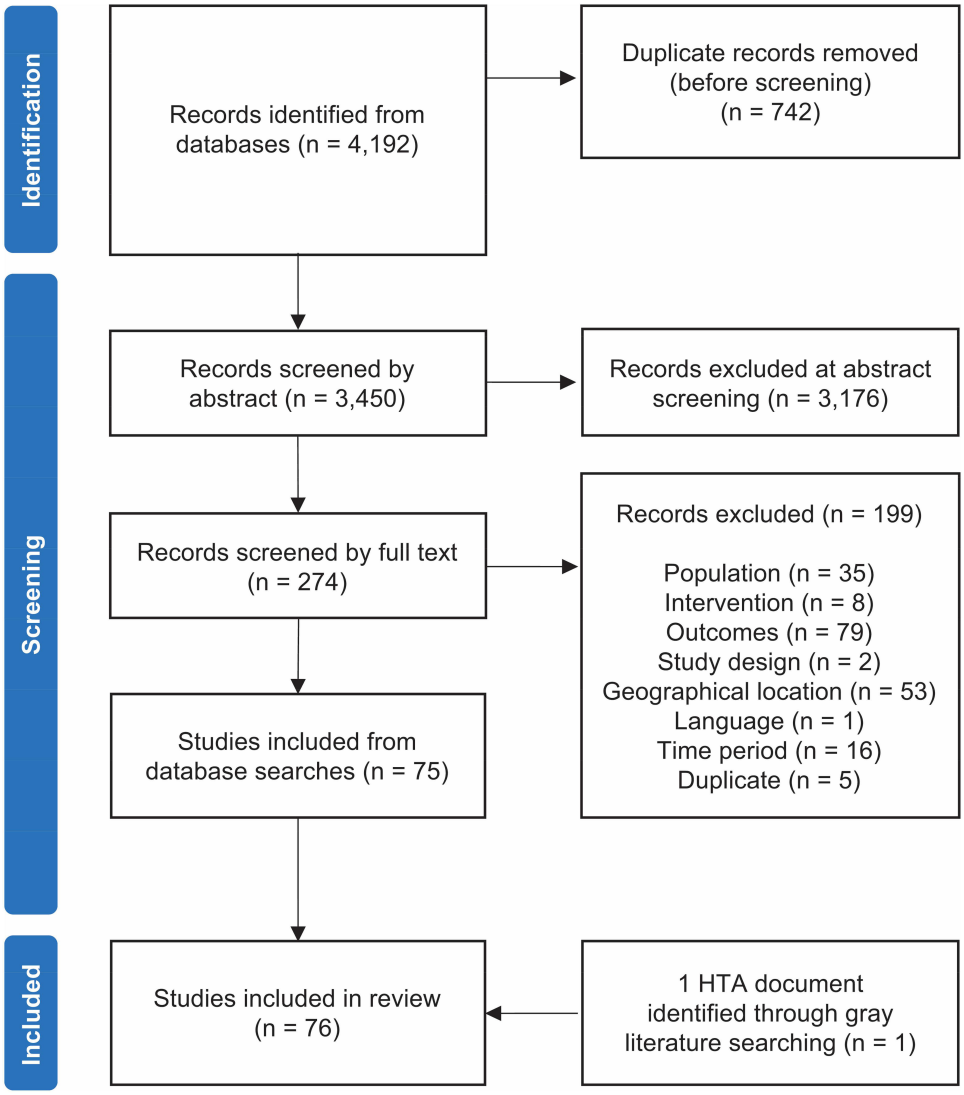

Figure 1 Flow diagram of included studies.
Abbreviation: HTA, health technology assessment.

Overall Survival

Most of the identified studies reported on OS (n=48).[2,25–71] The definition of OS varied across studies: 12 studies defined OS as "time from date of RC to date of last follow-up or death from any cause";[27,29,34,44,45,48,52,60,64–66,68] 10 defined OS as "time elapsed from cancer diagnosis until death or last follow-up";[28,31,32,37,39,41,42,46,49,54] 4 studies used other definitions of OS;[30,43,56,61] and most studies (n=22) did not specify the definition of OS used.[2,25,26,33,35,36,38,40,47,50,51,53,55,57–59,62,63,67,69–71]

The range of reported OS rates at 3 years and 5 years and median OS for patients treated with RC alone, NAC+RC, or RC+AC are shown in Figure 2, with details provided in Supplementary Table 1. Across studies, 3-year OS rates ranged from 44.9% to 78.5% among patients treated with RC alone, from 34.5% to 94.4% among patients treated with NAC+RC, and from 46.5% to 55.1% among patients treated with RC+AC. The 5-year OS rates ranged from 29.6% to 68.0% among patients treated with RC alone, from 30.2% to 76.9% among patients treated with NAC+RC, and from 33.2% to 50.0% among patients treated with RC+AC. The range of reported median OS was 0.7 to 8.3 years with RC alone, 1.8 to 7.5 years with NAC+RC, and 1.5 to 6.1 years with RC+AC. The definition of OS did not appear to substantially affect the range of reported OS between studies.

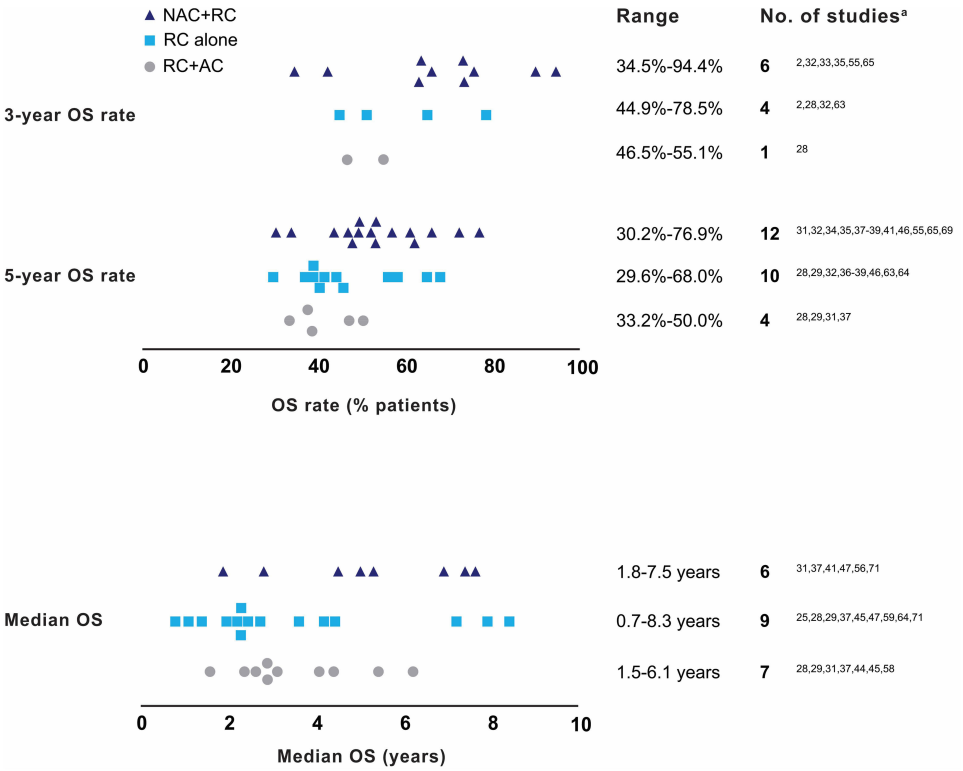

Figure 2 Range of overall survival estimates in identified publications. [a]Some studies reported more than one estimate.
Abbreviations: NAC, neoadjuvant chemotherapy; No., number; OS, overall survival; RC, radical cystectomy.

Two studies reported OS data for both US patients with MIBC who received NAC+RC and US patients with MIBC who received RC+AC. Macleod et al reported that in unadjusted analysis patients who received RC+AC had worse OS outcomes than patients treated with NAC+RC (HR, 1.40; 95% CI, 1.23–1.60); however, the authors note significant selection bias and that this difference was no longer seen in adjusted analysis.[30] Meanwhile, Tan et al reported that RC+AC had an equivalent survival benefit to that of NAC+RC (5-year adjusted OS: 50% [95% CI, 0.48–0.53] vs 53% [95% CI, 0.50–0.56], P=0.291).[31]

Progression-Free Survival

Three studies reported on PFS outcomes, with PFS defined as time from the start of NAC (for patients treated with NAC+RC) or RC (for patients treated with RC alone), until disease progression or death,[58,62,70] including one study comparing NAC+RC with RC alone.[70] In that study, risk of progression was lower with NAC+RC than RC alone (HR 0.44, 95% CI, 0.21–0.94).[70] Another study reported that for patients receiving RC+AC, those who received AC ≤90 days post-surgery had higher median PFS than those who received AC >90 days post-surgery (35 months vs 24 months), although this difference was not statistically significant.[58]

Recurrence-Free Survival

RFS was defined across publications as the time from RC to clinical recurrence or last follow-up. Four US studies[32,42,64,72] and 1 multinational study[59] reported on RFS. Among these, Boeri et al reported in a retrospective US study that 5-year RFS was highest, 56.2%, among patients who underwent >3 cycles of NAC (defined in the study as "optimal NAC", in accordance with treatment guideline recommendations of 3–4 cycles,[4,7] and including cisplatin- and carboplatin-based regimens).[32] Five-year RFS was 48.9% in patients who did not receive NAC and 46.8% in patients who underwent <3 cycles of NAC (defined as "suboptimal").[32] Tachibana et al reported median RFS among US patients who received RC alone. In this study, median RFS was 22.1 months for patients with pT2b staging (muscle invasion

through greater than 50% of the muscularis propria) and 30.9 months for patients with pT2a staging (muscle invasion through less than 50% of the muscularis propria).[64] Finally, Marcq et al reported 3-year and 5-year RFS of 24% and 20%, respectively, among patients with positive surgical margins who underwent RC alone for MIBC.[59]

Metastasis-Free Survival

MFS, defined from randomization to the first evidence of metastatic disease or death, was reported in 2 studies.[59,71] Marcq et al reported that median MFS was 12 months among patients who received RC and had positive surgical margins.[59] Meanwhile, Hensley et al reported that patients who underwent NAC+RC had longer MFS compared with patients who received RC alone (76.6 months vs 69.7 months).[71]

Time From Last Cycle of NAC to RC

Four studies reported on time from the last cycle of NAC to RC.[35,40,41,73] Three of these reported that a delay from NAC to RC longer than 8–12 weeks was associated with disease progression or increased mortality.[35,41,73] For example, Boeri et al reported that patients with time to RC ≤10 weeks had significantly lower mortality than patients with time to RC >10 weeks.[35]

Economic Burden

There were 12 studies identified that reported economic burden among patients with MIBC receiving RC[39,51,57,74–82] (9 of which were from the US[39,51,74–80]), with 7 reporting direct costs (6 from the US and 1 from France) and 5 reporting on length of hospital stay (3 from the US, 1 from Germany, and 1 from the EU) following treatment.

A summary of the direct costs associated with MIBC for patients who underwent RC is shown in Table 2.[74–79,81] Among the US studies, Leow et al found that the majority of 90-day hospital costs consisted of index hospitalization costs ($34,803 of $39,651).[75] Meanwhile, Golla et al reported that costs associated with RC over 2 and 5 years in the US consisted of mostly outpatient costs. For patients treated with RC alone, outpatient costs made up $100,900 out of $191,363 total costs over 2 years with RC.[79] Negrier et al reported mean costs in France for a hospital stay that included RC for patients with MIBC were €13,184.[81]

The median length of hospital stay for patients with MIBC undergoing RC ranged from 5.0 to 9.6 days,[39,51,74,80,82] and the median length of an intensive care unit (ICU) stay was reported as 3 days[57] (Supplementary Table 2). One study by Posielski et al reported a longer median length of stay (9.6 days) for RC alone compared with NAC+RC (8.5 days) among patients aged ≥70 years ($P<0.001$) and found NAC to be an independent predictor of shorter length of stay in adjusted regression analysis.[39]

Humanistic Burden

Humanistic burden was reported in 5 cohort studies: 1 in the US and 4 in Germany (Table 3).[83–87] In each of these studies, the main instrument used to measure humanistic burden was the European Organization for Research and Treatment of Cancer core questionnaire (EORTC-QLQ-C-30), which assesses different aspects of quality of life of cancer patients.[88] Other instruments included questionnaires specific to MIBC (EORTC-QLQ-BLM-30),[89] bladder cancer (Functional Assessment of Cancer Therapy–Bladder, FACT-Bl),[90] incontinence (International Consultation on Incontinence Questionnaire–Urinary Incontinence Short Form [ICIQ-SF]),[91] or stress (Questionnaire on Stress in Cancer Patients [QSC-R10]).[92]

Health-related quality of life (HRQOL) has been assessed over the course of treatment with NAC+RC or RC alone during a follow-up period of 1 to 12 years.[83–87] Feuerstein et al reported that prior to RC, patients treated with NAC had marginally better emotional and mental health than patients who did not receive NAC; however, they saw no differences between treatment groups in the other HRQOL items measured.[83] Preoperatively, Volz et al reported that fatigue and appetite loss were among the common symptoms affecting patient quality of life and that these symptoms diminished during the 2 years post-RC.[86] Bahlburg et al saw an improvement in HRQOL during 1-year post-RC, but reported that around 40% of patients had high psychosocial distress at all time points up to 1 year post-RC.[87] Kretschmer et al saw good general HRQOL 2 years post-RC among 32.4% of patients with ileal conduit urinary diversion and 61.1% of

Table 2 Economic Burden: Costs

Author/Year	Study Details (Country/Region, Study Type, Patient Population, N, Cost Year)	Costs
Leow (2018)[75]	• US • Cohort study • Patients who received RC • N=23,173 • Cost year 2016	• 90-day direct hospital costs post-RC, $39,651, of which index hospitalization costs were $34,803 and post-discharge readmission costs were $4847
Williams (2019)[78]	• US • Population-based cohort study • Patients aged 66–85 with MIBC who received RC • N=2963 • Cost year not reported	• Median costs at 90 days with RC, $68,692 • Median costs at 180 days with RC, $109,078 • Median costs at 365 days with RC, $148,757
Bagheri (2021)[76]	• US • Retrospective claims • Patients aged 66–85 with MIBC who received RC or partial cystectomy • N=2305 • Cost year 2019	• Total costs per year for patients with RC, $143,831 • Total costs per year for patients with PC, $107,359
Poretta (2021)[74]	• US • Patients with MIBC undergoing RC • N=855 • Cost year 2019	• Medical and drug costs after surgery $15,637 and $16,009 per patient per month among patients without reported NAC • Among patients who developed metastatic disease, average monthly costs were $50,161
Golla (2022)[79]	• US • Cohort claims study • Patients aged 66–89 with MIBC who received RC • Costs at 2 and 5 years post-operation • N=2537 • Cost year not reported	• Total 2-year median costs for RC, $191,363 • Total 5-year median costs for RC, $253,651 • Inpatient 2-year median costs for RC, $62,240 • Inpatient 5-year median costs for RC, $75,499 • Outpatient 2-year median costs for RC, $100,900 • Outpatient 5-year median costs for RC, $146,561
Negrier (2022)[81]	• France • French hospitalization database • Monthly follow-up costs • Patients with MIBC and upper tract urothelial cancer • N=3370 • Cost year 2020	• Mean hospital stay with RC per patient with MIBC, €13,184 • Mean monthly costs per patient, €3313
Washington (2022)[77]	• US • Patients who received RC • Health plan and out-of-pocket costs from index admission to 90 days after • Retrospective claims • N=141,903 • Cost year not reported	• 90-day mean health plan cost for acute inpatients, $24,643 • Mean out-of-pocket costs for acute inpatients, $1428 • Mean ER costs, $182 • Mean office visit costs, $1127

Abbreviations: ER, emergency room; MIBC, muscle-invasive bladder cancer; MIUC, muscle-invasive urothelial carcinoma; NAC, neoadjuvant chemotherapy; PC, partial cystectomy; RC, radical cystectomy.

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Table 3 Humanistic Burden

Author/Year	Study Details	Questionnaire Used	Instrument Measurement	Observations
Feuerstein (2019)[83]	• US • Cohort study • Patients with MIBC scheduled for RC • Data collected within 4 weeks of scheduled RC • N=155	• EORTC-QLQ-C30 • EORTC-QLQ-BLM30	• HRQOL for patients treated with NAC prior to RC	• No significant difference regarding general HRQOL between NAC-treated and untreated patients prior to RC • Marginally better emotional and mental health in patients with vs without NAC
Kretschmer (2020)[84]	• Germany • Prospective cohort study • Patients with MIBC undergoing RC (IC and ONB) • Follow-up data collected 3, 12, and 24 months after RC • N=134	• EORTC-QLQ-C30	• Quality of life of cancer patients	• 2 years postoperatively general HRQOL was greater in the ONB patient cohort compared with the IC cohort • Good general HRQOL was reached by 32.4% of patients in the IC cohort and 61.1% of patients in the ONB cohort • Significantly better physical and role functioning in the ONB patient cohort in comparison with the IC cohort
Schulz (2021)[85]	• Germany • Cohort study • Patients with MIBC undergoing RC (IC and ONB) • Follow-up period from 3 months to 12 years after receiving RC • N=280	• EORTC-QLQ-C30 • ICIQ-SF	• Impact of symptoms of incontinence on outcome	• Decision regret was reported among the ONB patient cohort following ONB urinary diversion. This was reported between the 4- and 6-year time points, without any correlation with general HRQOL
Volz (2022)[86]	• Germany • Cohort study • Patients with MIBC scheduled for RC (IC and ONB) • Data collected preoperatively and at 3, 12, 24, 36, and 48 months of follow-up • N=246	• EORTC-QLQ-C30 • EORTC-QLQ-BLM-30 • FACT-BI	• Quality of life of cancer patients • Impact of RC and reconstructive surgery in terms of HRQOL • Bladder cancer-specific symptoms	• No statistical differences between IC and ONB patient cohorts postoperatively in terms of EORTC-QLQ-BLM-30 assessments • Significant differences between IC and ONB patient cohorts regarding preoperative EORTC-QLQ-C30 symptoms and functioning scores were reported including increased fatigue and appetite loss, which diminished during the postoperative time course • No significant differences across IC and ONB patients at various time points, up to 48 months
Bahlburg (2023)[87]	• Germany • Cohort study • Patients who had received RC and now receiving inpatient rehabilitation after RC (IC and ONB) • Follow-up data collected 4 weeks, 6 and 12 months after RC • N=842	• QSC-R10 • EORTC-QLQ-C30 • EORTC-QLQ-BLM-30	• Psychosocial distress and quality of life in cancer patients	• HRQOL improved during follow-up after RC • An average of 40% of all participants (consisting of IC and ONB cohorts) reported high psychosocial distress at all time points, up to 1 year

Abbreviations: EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC-QLQ-BLM-30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Muscle-Invasive Bladder Cancer 30; FACT-BI, Functional Assessment of Cancer Therapy–Bladder; HRQOL, health-related quality of life; IC, ileal conduit; ICIQ-UI SF, International Consultation on Incontinence Questionnaire–Urinary Incontinence Short Form; MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy; ONB, orthotopic neobladder; QSC-R10, Questionnaire on Stress in Cancer Patients; RC, radical cystectomy.

patients with orthotopic neobladder.[84] Over the longer term, up to 12 years, Schulz et al reported that patients who had RC and orthotopic neobladder experienced decision regret (mainly driven by incontinence) that peaked between 4 and 6 years post-surgery, without any effect on their general HRQOL.[85]

Discussion

An understanding of real-world outcomes with current systemic therapies for MIBC will help to contextualize data from clinical trials for approved and guideline-recommended treatments and emerging therapies. This is particularly important in the context of the changing treatment landscape for this disease and the recent emergence of new therapies, such as adjuvant nivolumab and perioperative durvalumab in addition to NAC.[93] However, there are challenges in comparing outcomes across real-world studies, due to, for example, differing study designs and incomplete or varied definitions of outcomes. This SLR sought to address this gap by summarizing the available real-world data to describe treatment effectiveness and economic and humanistic burden for patients with RC with or without neoadjuvant or adjuvant systemic therapy.

The identified real-world studies show that NAC or AC may improve survival outcomes in some patients compared with RC alone.[28,31,32,70,71] The trend of improved outcomes with NAC from real-world data complements the data from clinical trials, which showed significant improvements in OS with NAC following RC compared with RC alone.[8,94] For example, a meta-analysis of 11 clinical trials showed an HR of 0.86 (95% CI, 0.77–0.95, P=0.003), improving OS from 45% to 50% at 5 years.[8,94] This included one trial that reported improvement of OS from 3.8 to 6.4 years in patients receiving NAC+RC compared with RC alone.[95] Evidence for efficacy of AC from clinical trials, while not as clear as the evidence for NAC, also supports its use in certain patients at high risk of relapse.[5] A meta-analysis of 9 clinical trials demonstrated significant improvement over RC (HR=0.77; 95% CI, 0.59–0.99; P=0.049), translating to a 23% decrease in risk of death with AC compared with controls.[4,10]

However, data reported in this SLR suggest that for many patients, survival remains poor, with OS ranging from 1 to 7 years and 5-year disease recurrence in >44% of patients following RC with or without NAC or AC.[25–29,31,32,37,41–45,47,53,56,58] At the same time, utilization of NAC or AC is low (<40%) in patients with MIBC,[13–15] suggesting there remains an unmet need for systemic treatments that are both better tolerated and can improve survival outcomes over those of existing therapies. This is particularly true for the >50% of patients who are not eligible for cisplatin-based therapies,[96] as there are currently very limited standard-of-care or systemic treatment options that have been shown to improve survival in this population. Emerging therapies and novel treatment paradigms may help to address this gap.

The results of this SLR indicate that patients with MIBC who receive RC either with or without NAC or AC experience a high economic burden. Across studies, RC was associated with high costs, up to around one-third of which were attributable to inpatient costs.[79] Hospital stays for RC had a median length between 5 and 10 days and cost upwards of $34,000 in the US[75] and €11,700 in France.[81] Given the differences in country, cost year and methodology, direct comparisons between the studies are limited. The difference in costs between studies in the US and France may reflect differences in clinical practice between the regions or may be related to differences in study design or the overall higher health spending in the US.[97] Other key cost drivers across the identified studies included medical and subsequent treatment costs post-surgery, ICU/emergency room admissions, and hospital specialist visits. None of the identified studies reported data on drug costs, which would be a useful subject for future investigations.

There were not many studies addressing the humanistic burden of patients with MIBC treated with RC; the majority of these studies were from Germany, and only one US study reported on humanistic burden.[83] The available studies suggest that common symptoms affecting quality of life included fatigue and appetite loss, which improved during 1 to 2 years after surgery, but that HRQOL remained low and psychosocial stress remained high for approximately 40% of patients during this time period.[84,87] Further studies are needed to confirm the humanistic burden of RC and systemic therapies among patients with MIBC in the US and to better distinguish between burden due to treatment and burden due to disease progression.

Limitations

This study was limited to the publications available at the time of the search and may be subject to publication bias. Furthermore, no real-world studies were identified on nivolumab at the time of searching; however, nivolumab was approved as an adjuvant therapy for some patients after RC in 2021 in the US and in 2022 in Europe and will be important to consider in the current disease landscape.[98–100] Changes in the management of patients over recent years, including the introduction of robotic cystectomy and use of enhanced recovery after surgery (ERAS) protocols, may also be expected to reduce length of hospital stays for patients with MIBC who receive RC and who may not have been captured in the available studies.[101,102] In addition, the study also included conference abstracts, which may not have been subject to peer review. From a global perspective, the SLR focused on studies conducted in the US, the UK, and the EU 4 (Germany, France, Spain, and Italy), with the majority of identified studies coming from the US, so may not be representative of the rest of the world. Furthermore, the SLR included publications in only the English language, so there is a risk that relevant, non-English language publications may not have been included. Similarly, studies that had fewer than 100 patients were excluded, and there is a subsequent risk that small studies that are still relevant were not included; however, they would be of small sample size, and larger observational studies were available.

It should also be noted that this SLR focused on patients who received RC; thus, studies that reported on patients who underwent bladder-sparing treatment or studies in which the treatment was unclear, were excluded at the abstract screening stage. That population will need to be examined in greater detail to fully understand the treatment landscape for patients with MIBC. There was also likely to be a selection bias in real-world observational studies looking at patients who did or did not receive NAC, since patients eligible for NAC may have a lower comorbidity burden than those who are not eligible, which may bias survival results in favor of patients receiving NAC. Some studies included patients who were treated with chemotherapy regimens that are not recommended by treatment guidelines, such as NAC with carboplatin rather than cisplatin. In these cases, the reported survival outcomes may be lower than if treatment guidelines had been followed. Finally, none of the identified studies included costs specific to systemic treatment, so it is not possible to discuss the economic burden of these therapies directly.

Conclusion

Real-world studies have reported modestly longer survival with NAC or AC over RC alone; however, the data demonstrate that OS remains poor and rates of disease recurrence are high. The low eligibility for and utilization of NAC or AC, coupled with the substantial economic burden for patients with MIBC, suggest that more effective therapies are needed. New approaches, such as adjuvant immunotherapy, perioperative immunotherapy plus neoadjuvant chemotherapy, and novel systemic therapy regimens currently in clinical trials (eg, perioperative antibody–drug conjugate plus immunotherapy combinations) may help to address this gap.

Ethics Approval and Informed Consent

This review used only previously published data and ethical approval was not required.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Lei Yin and Heidi S. Wirtz are employees of and hold stock in Pfizer Inc. At the time of this study, Vanessa Shih was an employee of Pfizer Inc.

Eleni Theodorou, Ryan Dillon, and Sam Brancato are employees of Astellas Pharma Inc.

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The authors report no other conflicts of interest in this work.

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