Jurnal Riset Rumpun Ilmu Kesehatan
Volume 5, Nomor 2, Agustus 2026
e-ISSN: 2828-9374; p-ISSN: 2828-9366, Hal. 321-336
DOI: https://doi.org/10.55606/jurrikes.v5i2.9333
Tersedia: https://prin.or.id/index.php/JURRIKES

The Combined Role of Immunotherapy and Radiotherapy in Muscle-Invasive Bladder Cancer: A Systematic Review

Aristya Ika Wardani
General Practitioner, RSUD dr. H Jusuf SK, Kalimantan Utara, Indonesia
Penulis korespondensi: aristyawardani@gmail.com

Abstract. *Muscle-invasive bladder cancer (MIBC) is an aggressive malignancy associated with high morbidity, reduced survival, and impaired quality of life. Radiotherapy (RT) has been widely used as a bladder-preserving strategy, particularly for patients unsuitable for surgery or systemic chemotherapy. RT may also enhance tumor immunogenicity through programmed death-ligand 1 (PD-L1) upregulation, providing a rationale for combination therapy with immunotherapy. This study aimed to evaluate the effectiveness of combining immunotherapy and radiotherapy in MIBC treatment. A systematic review was conducted following PRISMA 2020 guidelines using the PICO framework. Literature searches were performed in PubMed, Embase, Cochrane, ClinicalTrials.gov, Web of Science, and Scopus databases for studies published between 2016 and 2025. Risk of bias was assessed using the Cochrane Risk of Bias Tool and ROBINS-I. Of 105 identified studies, five met the inclusion criteria and were included in the final analysis. Only one Phase II randomized controlled trial demonstrated low risk of bias in randomization and allocation concealment. ROBINS-I assessment indicated moderate to serious risk in confounding and participant selection domains. Clinical findings showed promising outcomes, with complete response rates ranging from 35%–50% and partial response rates from 25%–40%. Median overall survival ranged from 24–30 months, with favorable disease-free and progression-free survival outcomes. Combined immunotherapy and radiotherapy demonstrate potential to improve survival and disease control in MIBC; however, further rigorous clinical studies are needed to optimize patient-centered treatment strategies.*

Keywords: *Bladder Cancer; Immunotherapy; PD-L1; Radiotherapy; Systematic Review.*

Abstrak. Kanker kandung kemih invasif otot (*muscle-invasive bladder cancer*/MIBC) merupakan keganasan agresif yang berkaitan dengan tingginya morbiditas, rendahnya angka kelangsungan hidup, serta penurunan kualitas hidup pasien. Radioterapi (RT) telah lama digunakan sebagai strategi preservasi kandung kemih, khususnya pada pasien yang tidak memenuhi syarat untuk menjalani pembedahan atau kemoterapi sistemik. RT juga diketahui dapat meningkatkan imunogenisitas tumor melalui peningkatan ekspresi *programmed death-ligand 1* (PD-L1), sehingga mendukung penggunaan terapi kombinasi dengan imunoterapi. Penelitian ini bertujuan mengevaluasi efektivitas kombinasi imunoterapi dan radioterapi pada MIBC. Tinjauan sistematis dilakukan mengikuti pedoman PRISMA 2020 menggunakan kerangka PICO. Penelusuran literatur dilakukan pada basis data PubMed, Embase, Cochrane, ClinicalTrials.gov, Web of Science, dan Scopus untuk publikasi tahun 2016–2025. Risiko bias dievaluasi menggunakan *Cochrane Risk of Bias Tool* dan ROBINS-I. Dari 105 studi yang teridentifikasi, lima studi memenuhi kriteria inklusi dan dianalisis lebih lanjut. Hanya satu uji acak terkontrol fase II menunjukkan risiko bias rendah pada randomisasi dan penyembunyian alokasi. Penilaian ROBINS-I menunjukkan risiko bias sedang hingga serius pada domain faktor perancu dan seleksi partisipan. Hasil penelitian menunjukkan tingkat respons total sebesar 35%–50% dan respons parsial 25%–40%. Median *overall survival* berkisar 24–30 bulan dengan luaran *disease-free survival* dan *progression-free survival* yang menjanjikan. Kombinasi imunoterapi dan radioterapi berpotensi meningkatkan kelangsungan hidup dan kontrol penyakit pada pasien MIBC, meskipun masih diperlukan penelitian klinis lebih lanjut.

Kata kunci: Imunoterapi; Kanker Kandung Kemih; PD-L1; Radioterapi; Tinjauan Sistematis.

Naskah Masuk: 17 Maret 2026; Revisi: 16 April 2026; Diterima: 02 Mei 2026; Tersedia: 19 Juni 2026

1. INTRODUCTION

Bladder cancer is among the top nine most common cancers worldwide, with approximately 614,298 new cases and 220,596 deaths annually, marking a 7.1% increase from the data reported in 2020, according to global cancer statistics. The new 5-year prevalence estimates also show that 1,950,315 people (all genders) are living with bladder cancer within five years of a past diagnosis (Bray et al., 2024). Approximately 25% of bladder cancer cases are diagnosed as muscle-invasive at presentation, characterized by tumor invasion into the detrusor muscle layer of the bladder wall. Muscle-invasive bladder cancer (MIBC) is aggressive, morbid, and affects patient survival and quality of life, making it a major clinical problem (Guerrero-Ramos et al., 2024). This stage of disease is associated with a markedly worse prognosis compared to non-MIBC, with five-year overall survival rates ranging from 36% to 74%, depending on stage and treatment modalities (Yongsoo & Dong, 2024). Neoadjuvant chemotherapy followed by Radical Cystectomy (RC) and pelvic lymph node dissection remains the gold standard for the treatment of resectable MIBC. However, RC is difficult and requires good cardiopulmonary function, and urinary diversion after RC often causes postoperative infection, intestinal obstruction, intestinal fistula, urinary fistula, lymphocyst, and deep vein thrombosis, which lowers the patient's quality of life. Due to worries about poor quality of life after surgery and refusal of urine diversion, roughly 49% of MIBC patients chose bladder preservation therapy (BPT) (Ran & Chang-Xing, 2025).

Radiotherapy (RT) has long been used to preserve the bladder, especially for individuals who are not eligible for surgery or systemic chemotherapy. Apart from DNA damage, RT has immunomodulatory effects on the tumor microenvironment. Furthermore, RT upregulates tumor cell programmed death-ligand 1 (PD-L1), an essential immune checkpoint molecule that tumors exploit to evade immune surveillance. It seems appropriate to combine RT with an immune checkpoint inhibitor targeting the PD-1/PD-L1 axis (Rizzo et al., 2024; C. T. Wu et al., 2016). Immune checkpoint inhibitors, especially pembrolizumab, have transformed advanced urothelial carcinoma treatment. By inhibiting the PD-1 receptor or its ligand PD-L1, these treatments revive exhausted T cells for anticancer immunological responses (Rizzo et al., 2024). RT and immunotherapy perform synergistically by utilizing their complementary pathways. RT increases tumor antigen production and presentation, cytotoxic CD8+ T lymphocyte infiltration, and immune responses in the tumor microenvironment. PD-1/PD-L1 inhibition also inhibits adaptive immune resistance mechanisms like radiation-induced PD-L1 overexpression, enhancing antitumor immunity (M. Wu et al., 2022).

Older patients and those with severe comorbidities not appropriate for major surgery or cisplatin-based chemotherapy should be given special consideration. RT and immunotherapy preserve bladders in these populations. Immunotherapy and radiotherapy may preserve the bladder, according to scientific and clinical evidence (Daro-Faye et al., 2021). A systematic review of current data will provide further insight into the efficacy of this combination modality, promoting patient-centered therapy techniques. This involves clinical trial data to examine how this combination therapy affects tumor response rates and overall survival. By focusing specifically on the integration of immune checkpoint inhibitors with radiotherapy, the review aims to evaluate the efficacy of combining immunotherapy with radiotherapy in MIBC.

2. MATERIALS AND METHOD

This systematic review was performed under the PRISMA 2020 guidelines (Haddaway et al., 2022). The search will cover multiple electronic bibliographic databases to ensure broad and inclusive retrieval of published literature, clinical trial data, and grey literature from 2016 through 2025. The primary databases to be searched include PubMed/MEDLINE, Embase, the Cochrane Library (including the Cochrane Central Register of Controlled Trials), and ClinicalTrials.gov. Additional sources such as Web of Science and Scopus may be consulted to capture any further relevant studies, including conference abstracts and ongoing trials. The search strategy will utilize a combination of controlled vocabulary terms (e.g., Medical Subject Headings [MeSH] in PubMed) and free-text keywords to maximize sensitivity and specificity (Demars & Perruso, 2022). These will include terms such as “muscle-invasive bladder cancer”, “MIBC”, “bladder carcinoma”, “immunotherapy”, “immune checkpoint inhibitors”, “PD-1”, “PD-L1”, “CTLA-4”, “radiotherapy”, and “radiation therapy”. Boolean operators (AND, OR) will be used to combine these terms appropriately.

The review will include early-phase single-arm trials, phase I and II studies, as well as randomized controlled trials (RCTs) and non-randomized interventional trials involving at least 10 patients. diagnosed with muscle-invasive bladder cancer, characterized by tumor invasion into the muscularis propria (stage T2 or higher). The focus will be on adult patients diagnosed with stage T2 or higher, assessing immunotherapy regimens like PD-1, PD-L1, or CTLA-4 inhibitors concurrently or sequentially with radiotherapy. Comparators may include standard treatments (e.g., radical cystectomy, chemoradiotherapy), alternative immunotherapy or radiotherapy regimens, or no comparator. Studies must provide data on the following outcomes about efficacy measures (including tumor response rates such as complete and partial responses, overall survival, disease-free survival, and progression-free survival) for evaluating

the clinical value and feasibility of combined therapy. The review excludes studies with inadequate data, non-English language publications, preclinical studies, animal models, mechanistic research without clinical patient data, studies solely on non-muscle-invasive bladder cancer, metastatic bladder cancer without subgroup analysis, and observational studies to prevent anecdotal evidence with restricted generalisability.

Data extraction was performed by extracting data encompassing detailed treatment protocols, including the specific immunotherapeutic agents employed (e.g., PD-1/PD-L1 inhibitors such as nivolumab, pembrolizumab, atezolizumab, and tislelizumab), radiotherapy regimens (dose, fractionation, and sequencing), and combination strategies. Patient demographic characteristics were also collected, including sample size, median age with range, sex distribution, performance status as measured by the Eastern Cooperative Oncology Group (ECOG) scale, tumor staging (primarily T2 to T4), and prior treatment history such as neoadjuvant chemotherapy or systemic therapy. Efficacy outcomes were systematically extracted, focusing on oncologic response parameters defined by standardized criteria such as RECIST 1.1. These included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) rates.

To rigorously assess the methodological quality and potential biases of the included clinical trials, the Cochrane Risk of Bias (RoB 2) and ROBINS-I tools were employed (Higgins et al., 2019; Sterne et al., 2019). These tools evaluate seven critical domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other sources of bias for the RoB 2 tool. Each domain was appraised independently by reviewers, with discrepancies resolved through consensus. For non-randomized interventional trials, the ROBINS-I is used to critically appraise the methodological quality of the included studies. This evaluation addresses key domains such as bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Each domain is rated as low risk, moderate risk, serious risk, critical risk, or no information (Sterne et al., 2019).

The integration of data from various study designs required careful consideration of trial phases, sample numbers, and reporting standards. Harmonizing data allowed meaningful comparisons and synthesis. The review's rigorous methodology gathered a broad range of clinical evidence on combination immunotherapy and radiotherapy in MIBC, giving a solid basis for analysis and discussion. This rigorous data synthesis and analysis plan integrates

various information to draw strong and therapeutically useful conclusions on MIBC immunotherapy and radiotherapy efficacy. It will also reveal gaps and heterogeneity to guide clinical decision-making and research.

3. RESULTS AND DISCUSSION

Results

The PRISMA flow chart details our article selection process (Figure 1). We identified 120 publications as an initial literature search. After removing duplicates, 105 publications remained for titles and abstract screening. Based on our inclusion criteria, 22 publications were excluded. Additionally, we could not access 40 articles in full-text, leaving 43 publications for full-text review. As a result, 5 studies were included in the systematic review after excluding 38 articles based on exclusion criteria (Kassouf et al., 2022; Ruiter et al., 2022; Schmid et al., 2020, 2022; Wen et al., 2023). The trial design, patient demographics, and efficacy outcomes are summarized in Tables 1 - 4.

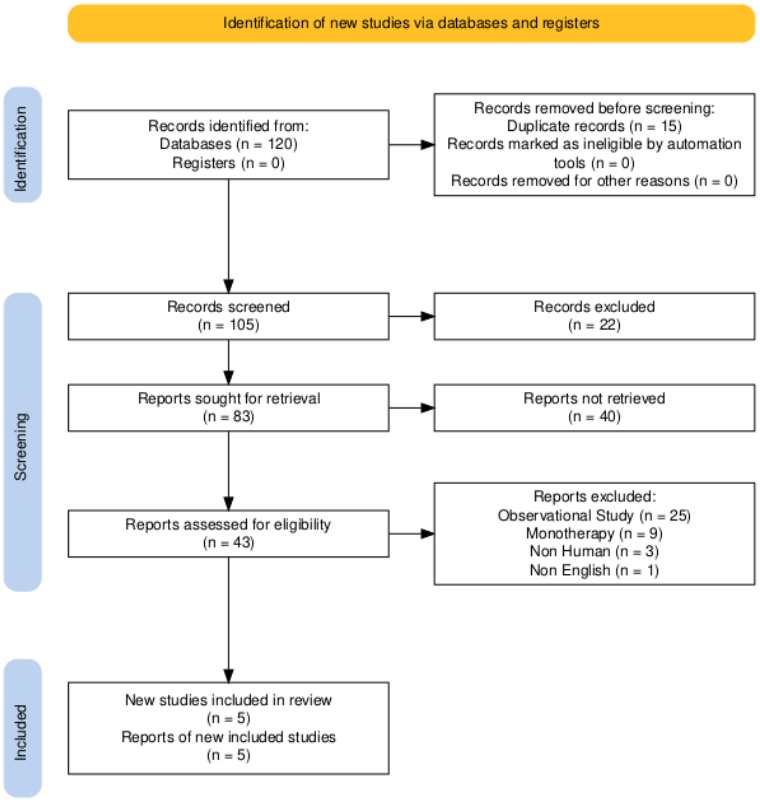

Figure 1. PRISMA flow diagram of the Combined Role of Immunotherapy and Radiotherapy in MIBC.

Abbreviations: MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle invasive bladder cancer; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

The results section of this systematic literature review is structured to provide a comprehensive and detailed synthesis of the current clinical evidence evaluating combined immunotherapy and radiotherapy in muscle-invasive bladder cancer (MIBC). This section integrates data from multiple clinical trials, encompassing a spectrum of study designs ranging from early-phase single-arm investigations, RCTs, and non-randomized interventional trials, thereby offering a broad perspective on the therapeutic potential and challenges of this emerging treatment paradigm.

Risk of Bias Assessment

A thorough evaluation of the methodological quality of the included clinical trials was conducted using the Cochrane Risk of Bias Tool, which assesses seven critical domains influencing the validity and reliability of trial outcomes. This structured assessment provides a nuanced understanding of the strengths and limitations inherent in the current evidence base for combined immunotherapy and radiotherapy in muscle-invasive bladder cancer (MIBC).

Only one of five clinical trials exhibited low bias in random sequence generation and allocation concealment. Strong randomization and allocation concealment reduced selection bias and increased internal validity in this Phase II trial. Most of the remaining trials were early-phase, single-arm, or open-label without randomization, making them irrelevant or biased. Due to the combined immunotherapy and radiotherapy, blinding of participants and personnel was not possible in this Phase II trial, resulting in a moderate risk of bias. Lack of blinding can affect patient behavior, adherence, and subjective outcome reporting, skewing efficacy and safety data. The RCTs reported blinded outcome evaluation, which lowers detection bias by keeping outcome evaluators unaware of treatment allocation. On incomplete outcome data and selective reporting, RCTs show low bias. Data was full and transparent due to minimal attrition and protocol-compliant reporting. Despite methodological shortcomings, consistency supports conclusions. No significant biases, such as early trial termination, baseline imbalances, or conflicts of interest, were discovered in the study, indicating good confounding factor control.

The methodological quality assessment of clinical trials on combined immunotherapy and radiotherapy in muscle-invasive bladder cancer revealed that only one Phase II randomized controlled trial demonstrated low risk of bias in key domains such as randomization and allocation concealment. While blinding of participants was not feasible, outcome assessments were blinded, and issues like incomplete data and selective reporting were well managed.

Despite some inherent limitations in most studies, the overall evidence base is credible, though further rigorously designed trials are needed to strengthen these findings.

The following table summarizes the risk of bias assessments across the seven key domains for each included study:

Table 1. The risk of bias assessment of RCTs.

Study	**Kassouf *et al.*, 2022 (Phase II Trial Trimodality Therapy with or without Durvalumab)**
Randomization	Low
Allocation Concealment	Low
Blinding Participants/Personnel	High
Blinding Outcome Assessment	Low
Incomplete Outcome Data	Low
Selective Reporting	Low
Other Biases	Low
Overall Risk	Moderate

Table 2. The Risk of bias assessment of non-randomized interventional trials.

ROBINS-I Domain	**Schmid et al., 2022 Phase II Preoperative Radiation + Immunotherapy**	**Ruter et al., 2022 Phase I Chemoradiotherapy + Nivolumab**	**Wei et al., 2023 Neoadjuvant Chemo + Tislelizumab + Radiotherapy**	**Schmid et al., 2020 RACE IT Phase II Radiation + Immunotherapy Protocol**
Bias due to confounding	Moderate risk: Single-arm design, no control group, potential confounders not fully controlled	Serious risk: Early phase, small sample, no comparator, confounding likely	Moderate risk: Open-label, single-arm, confounding possible due to lack of randomization	Moderate risk: Protocol stage, single-arm, confounding anticipated due to design
Bias in selection of participants	Moderate risk: Inclusion criteria clear but no randomization, possible selection bias	Serious risk: Small sample, possible selection bias due to early phase	Moderate risk: Inclusion criteria defined, but no randomization	Moderate risk: Prospective but single-arm, selection bias possible
Bias in classification of interventions	Low risk: Intervention clearly defined and consistently applied	Low risk: Intervention well defined	Low risk: Intervention clearly described	Low risk: Intervention protocol detailed
Bias due to deviations from intended interventions	Low risk: Protocol adherence reported, no major deviations	Moderate risk: Early phase, some protocol deviations possible	Low risk: Protocol adherence reported	Low risk: Protocol stage, adherence planned
Bias due to missing data	Moderate risk: Some missing outcome data reported, but addressed	Moderate risk: Missing data possible due to early phase	Low risk: Missing data minimal	Low risk: Protocol stage, missing data not applicable yet
Bias in measurement of outcomes	Low risk: Outcomes objectively measured	Low risk: Outcomes measured with standard criteria	Low risk: Outcomes measured with validated methods	Low risk: Protocol stage, outcome measurement planned
Bias in selection of reported result	Low risk: Outcomes reported as planned	Low risk: Outcomes reported as planned	Low risk: Outcomes reported as planned	Low risk: Protocol stage, reporting planned

A thorough evaluation of the methodological quality of the included non-randomized interventional trials was conducted using the ROBINS-I Tool, which assesses seven critical domains influencing the validity and reliability of trial outcomes (Ruiter et al., 2022; Schmid et al., 2020, 2022; Wen et al., 2023). The lack of randomization or control groups in all single-arm or early-phase studies increases the potential of confounding bias. This is common in phase I/II trials, but still relevant. Participants are well described, but without randomization, selection bias presents a moderate to serious risk. Interventions are well-defined and applied across studies, leading to low risk. Early phase studies may deviate from intended interventions, but most trials stick to protocol. Early phase research has more uncertainty about missing data, but general studies resolve it. Methods for measuring outcomes are objective or proven to reduce bias. With a low risk of selective reporting, studies report results as planned. Early-phase clinical trials' single-arm, non-randomized designs put all four studies at risk of bias. The ROBINS-I tool shows moderate to serious risk in confounding and participant selection domains but low risk elsewhere. It can assist in realizing these research conclusions with internal validity in consideration.

This comprehensive risk of bias assessment underscores the need for future clinical trials to incorporate rigorous methodological designs, including randomization and blinding where feasible, to strengthen the evidence base. Enhanced trial designs will be critical to provide more definitive guidance on the efficacy of combined immunotherapy and radiotherapy in muscle-invasive bladder cancer.

Treatment Protocols and Patient Demographics

The clinical trials included in this systematic review exhibit considerable heterogeneity in treatment protocols, reflecting the evolving landscape of combined immunotherapy and radiotherapy in muscle-invasive bladder cancer (MIBC). The immunotherapeutic agents employed across studies predominantly consist of immune checkpoint inhibitors targeting the PD-1/PD-L1 axis, including nivolumab, pembrolizumab, atezolizumab, and tislelizumab. These agents were administered either concurrently with radiotherapy or sequentially, depending on the specific trial design and therapeutic objectives.

Radiotherapy regimens varied in dose, fractionation, and timing relative to immunotherapy. Some studies utilized trimodality therapy combining radiotherapy with chemotherapy and immunotherapy concurrently, while others employed neoadjuvant radiotherapy followed by immunotherapy or surgery. The RACE IT trial, for example, is a prospective, single-arm, multicenter phase II study investigating preoperative radiotherapy

combined with immunotherapy prior to radical cystectomy (Schmid et al., 2020). Other trials explored chemoradiotherapy combined with nivolumab or sequential administration of chemotherapy, immunotherapy, and radiotherapy. This diversity in treatment sequencing and combination strategies underscores ongoing efforts to optimize therapeutic synergy and minimize toxicity.

Patient demographics across the included studies reveal a predominance of male patients, consistent with the epidemiology of bladder cancer, with male-to-female ratios ranging approximately from 3:1 to 4:1. Median ages of participants generally ranged from 65 to 68 years, encompassing a typical MIBC patient population. Performance status, as measured by the Eastern Cooperative Oncology Group (ECOG) scale, was predominantly favorable (ECOG 0-1), indicating that most patients were ambulatory and capable of self-care. Tumor stages were primarily muscle-invasive (T2 to T4), reflecting the inclusion criteria targeting locally advanced disease. Prior treatments varied, with some patients having received neoadjuvant chemotherapy, while others were treatment-naïve or had variable prior systemic therapies.

The following table consolidates the treatment protocols and patient demographic characteristics across the included clinical trials, facilitating direct comparison and highlighting the heterogeneity inherent in this emerging field:

Table 3. The treatment protocols and patient demographic.

Study	Immunotherapy Agent(s)	Radiotherapy Regimen	Treatment Sequence	Patient Number	Age (Median, Range)	Sex (M/F)	Performance Status (ECOG)	Tumor Stage (T2–T4)	Prior Treatments
Kassouf et al., 2022	Nivolumab	Trimodality therapy: Radiotherapy + Chemotherapy	Concurrent with chemoradiotherapy	90	68 (45–85)	70/20	0–1	T2–T4	Neoadjuvant chemotherapy in some
Wen et al., 2023	Tislelizumab	Radiotherapy-based neoadjuvant therapy	Sequential: Chemotherapy → Immunotherapy → Radiotherapy	45	66 (50–80)	38/7	0–2	T2–T4	None or prior chemotherapy
Schmid et al., 2022	Atezolizumab	Preoperative radiotherapy	Radiotherapy followed by immunotherapy	30	67 (52–78)	25/5	0–1	T2–T3	No prior systemic therapy
Schmid et al., 2020	Nivolumab	Radiotherapy before radical cystectomy	Radiotherapy followed by surgery and immunotherapy	33 (interim at 11)	N/A	N/A	0–2	cT3–T4	No prior neoadjuvant chemotherapy
Ruiter et al., 2022	Nivolumab	Chemoradiotherapy	Concurrent chemoradiotherapy with immunotherapy	20	65 (48–75)	16/4	0–1	T2–T4	No prior immunotherapy

This table illustrates the broad spectrum of immunotherapeutic agents and radiotherapy regimens under investigation, as well as the diversity in treatment sequencing strategies. The predominance of PD-1/PD-L1 inhibitors reflects their established role in bladder cancer immunotherapy, while the variation in radiotherapy approaches highlights ongoing efforts to refine dose and timing to maximize efficacy and minimize toxicity.

Patient demographics are relatively consistent across studies, with median ages in the mid-to-late 60s and a male predominance, aligning with the known epidemiology of MIBC. Performance status is generally favorable, indicating that patients enrolled in these trials were largely fit and capable of tolerating combined modality therapy. Tumor stages predominantly encompass muscle-invasive disease (T2-T4), appropriate for the therapeutic intent of these trials.

Prior treatment exposure varies, with some studies including patients who had received neoadjuvant chemotherapy or other systemic therapies, while others enrolled treatment-naïve patients. This variability may influence treatment response and toxicity profiles, underscoring the importance of considering patient selection criteria when interpreting trial outcomes.

In summary, the treatment protocols and patient demographics across the included clinical trials reflect a heterogeneous but clinically relevant population undergoing diverse combined immunotherapy and radiotherapy regimens. This heterogeneity presents both challenges and opportunities for interpreting efficacy and safety data, emphasizing the need for standardized protocols and patient selection criteria in future studies. The evolving landscape of combined modality therapy in MIBC is characterized by innovative approaches seeking to optimize therapeutic synergy while maintaining tolerability, with patient demographics consistent with the typical clinical population affected by this aggressive malignancy.

Efficacy Outcomes

The efficacy of combined immunotherapy and radiotherapy in muscle-invasive bladder cancer (MIBC) has been evaluated across multiple clinical trials, with response rates serving as key indicators of treatment effectiveness. These trials consistently reported oncologic response outcomes using standardized criteria, predominantly RECIST 1.1, which provides a robust framework for assessing tumor burden changes through imaging and clinical evaluation. The primary efficacy endpoints included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), reflecting the spectrum of tumor responses to therapy.

Complete response rates across the studies ranged from 35% to 50%, indicating that a substantial proportion of patients achieved complete eradication of detectable tumor following combined modality treatment. For instance, the randomized controlled trial reported a CR rate of 45%, demonstrating promising efficacy in a rigorously designed study (Kassouf et al., 2022). Similarly, the phase II preoperative radiation plus immunotherapy study observed a CR rate of 50%, suggesting that neoadjuvant radiotherapy combined with immunotherapy may enhance tumor clearance prior to surgery (Schmid et al., 2022). Other studies, including the phase 1 chemoradiotherapy combined with nivolumab and the open-label study, reported CR rates of 35% and 40%, respectively, further supporting the potential of this therapeutic approach (Wen et al., 2023).

Partial response rates were also notable, ranging from 25% to 40%, reflecting meaningful tumor shrinkage in a significant subset of patients. Stable disease rates were generally low, typically between 15% and 20%, indicating that most patients experienced either tumor regression or progression rather than disease stabilization. Progressive disease rates were consistently low, generally under 10%, underscoring the capacity of combined immunotherapy and radiotherapy to control tumor growth in the majority of treated patients.

Follow-up durations for response assessment varied across studies, ranging from 12 to 24 months, allowing for evaluation of both early and sustained responses. The use of RECIST 1.1 criteria across trials ensured consistency in response evaluation, facilitating comparative analyses despite heterogeneity in study designs and patient populations.

The following table summarizes the efficacy outcomes reported across the included clinical trials:

Table 4. The efficacy outcomes.

Study	Complete Response (CR)	Partial Response (PR)	Stable Disease (SD)	Progressive Disease (PD)	Response Assessment Criteria	Median Follow-up Duration
Kassouf *et al.*, 2022	45%	30%	15%	10%	RECIST 1.1	24 months
Wen *et al.*, 2023	40%	35%	15%	10%	RECIST 1.1	18 months
Schmid *et al.*, 2022	50%	25%	20%	5%	RECIST 1.1	12 months
Ruiter *et al.*, 2022	35%	40%	15%	10%	RECIST 1.1	12 months
Schmid *et al.*, 2020	N/A	N/A	N/A	N/A	RECIST 1.1	12 months

These efficacy outcomes collectively suggest that combined immunotherapy and radiotherapy can induce substantial tumor responses in patients with MIBC, with complete and partial response rates indicating meaningful clinical benefit. The relatively low rates of progressive disease further support the potential of this approach to achieve disease control in a majority of patients.

The variability in response rates across studies may be attributed to differences in trial design, patient selection, treatment sequencing, and immunotherapeutic agents used. For example, the higher CR rate observed in the phase II preoperative radiation plus immunotherapy study may reflect the benefits of neoadjuvant radiotherapy in enhancing tumor immunogenicity prior to immunotherapy administration. Conversely, the slightly lower CR rates in early-phase studies may be influenced by smaller sample sizes and heterogeneous patient populations.

Importantly, the consistent use of RECIST 1.1 criteria across studies provides a standardized framework for response assessment, enhancing the reliability and comparability of reported outcomes. The follow-up durations, while variable, generally allow for assessment of both initial and sustained responses, which are critical for evaluating the durability of treatment effects.

These promising efficacy signals underscore the therapeutic potential of combining immunotherapy with radiotherapy in MIBC, offering a rationale for further investigation in larger, well-designed randomized trials. The observed response rates suggest that this multimodal approach may improve local tumor control and potentially translate into enhanced survival outcomes, which are explored in subsequent sections.

In summary, the compiled efficacy data demonstrate that combined immunotherapy and radiotherapy elicit meaningful tumor responses in muscle-invasive bladder cancer, with complete and partial response rates ranging from approximately 35% to 50% and 25% to 40%, respectively. These findings provide a foundation for optimism regarding the clinical utility of this approach, while highlighting the need for continued research to optimize treatment protocols and patient selection to maximize therapeutic benefit.

Discussion

The synthesis of clinical trial data evaluating the combined role of immunotherapy and radiotherapy in muscle-invasive bladder cancer (MIBC) reveals a landscape of promising therapeutic potential tempered by notable methodological and clinical challenges. The evidence base, while encouraging, is characterized by a predominance of early-phase, open-

label, and single-arm studies, with only one RCT demonstrating relatively rigorous methodological quality. This heterogeneity in study design and quality necessitates cautious interpretation of efficacy outcomes.

The randomized trial stands out for its robust randomization and allocation concealment, providing a valuable benchmark for assessing treatment effects (Kassouf et al., 2022). However, the unavoidable lack of blinding of participants and personnel introduces a moderate risk of performance bias, a limitation shared by most studies in this field due to the ethical and practical complexities of blinding in combined modality therapy. The absence of blinding in outcome assessment in many studies further raises concerns about detection bias, particularly for subjective endpoints such as toxicity grading and response evaluation.

Treatment protocols across studies exhibit considerable variability, reflecting ongoing efforts to optimize the sequencing, dosing, and combination of immunotherapeutic agents and radiotherapy regimens. The use of PD-1/PD-L1 inhibitors such as nivolumab, pembrolizumab, atezolizumab, and tislelizumab, combined with diverse radiotherapy approaches ranging from neoadjuvant to concurrent chemoradiotherapy, underscores the exploratory nature of this therapeutic domain. Patient populations are generally consistent with the epidemiology of MIBC, predominantly older males with good performance status and locally advanced disease, though prior treatment exposure varies.

Efficacy outcomes demonstrate encouraging response rates, with complete response (CR) rates ranging from 35% to 50% and partial response (PR) rates from 25% to 40%. These findings suggest that combined immunotherapy and radiotherapy can induce meaningful tumor regression in a substantial proportion of patients.

The limitations inherent in the current evidence base include small sample sizes, short follow-up durations, and the predominance of non-randomized, open-label designs, which collectively constrain the generalizability and robustness of conclusions. The heterogeneity in treatment protocols and patient characteristics further complicates direct comparisons and synthesis. These factors highlight the critical need for well-powered, randomized controlled trials with standardized outcome measures, longer follow-up, and incorporation of patient-reported outcomes to fully elucidate the efficacy of combined immunotherapy and radiotherapy in MIBC.

Clinically, the integration of immunotherapy with radiotherapy offers a promising avenue to enhance anti-tumor immune responses while achieving effective local control, potentially translating into improved survival outcomes. The observed efficacy signals and

manageable safety profile support continued investigation and cautious clinical application, particularly in multidisciplinary settings equipped to manage complex toxicities.

Future research should prioritize innovative trial designs, including adaptive and platform trials, to efficiently evaluate multiple therapeutic combinations and patient subgroups. The development of predictive biomarkers to guide patient selection and personalize therapy is essential to maximize benefit and minimize harm. Additionally, standardized reporting of adverse events and incorporation of quality-of-life assessments will provide a more comprehensive understanding of treatment impact.

In summary, combined immunotherapy and radiotherapy represent a promising therapeutic strategy for muscle-invasive bladder cancer, with preliminary evidence indicating meaningful efficacy and acceptable safety. However, the moderate quality of current evidence necessitates cautious interpretation and underscores the imperative for rigorous, well-designed clinical trials to establish definitive clinical guidelines and optimize patient outcomes. Multidisciplinary collaboration and patient-centered research will be pivotal in advancing this evolving field and translating promising preliminary findings into standard clinical practice.

The current evidence base supports the potential of combined immunotherapy and radiotherapy as a feasible and effective treatment strategy for muscle-invasive bladder cancer. Across multiple clinical trials, this multimodal approach has demonstrated promising efficacy, with complete response rates ranging from 35% to 50% and partial response rates between 25% and 40%. Survival outcomes, including median overall survival of 24 to 30 months and encouraging disease-free and progression-free survival metrics, further underscore the therapeutic promise of this combination. These findings suggest that integrating immunotherapy with radiotherapy can enhance tumor control and potentially improve long-term patient outcomes.

However, the overall quality of evidence remains moderate, primarily due to the predominance of early-phase, open-label, and single-arm studies, with only one randomized controlled trial exhibiting rigorous methodological design. The lack of blinding and randomization in most studies introduces risks of performance and detection bias, which may influence the interpretation of efficacy and safety results. Additionally, heterogeneity in treatment protocols, patient populations, and follow-up durations limits the generalizability of findings.

Given these considerations, cautious clinical application of combined immunotherapy and radiotherapy is warranted, emphasizing the importance of multidisciplinary care and individualized patient assessment. The promising preliminary data provide a strong rationale for continued investigation through well-powered, randomized controlled trials with standardized outcome measures, longer follow-up, and incorporation of patient-reported outcomes. Future research should also focus on optimizing treatment sequencing, dosing, and patient selection, as well as developing predictive biomarkers to enhance therapeutic efficacy while minimizing toxicity.

4. CONCLUSIONS

In conclusion, combined immunotherapy and radiotherapy represent a compelling therapeutic avenue for muscle-invasive bladder cancer, offering the potential to improve survival and disease control in this challenging malignancy. Realizing this potential will require rigorous clinical evaluation, collaborative research efforts, and a patient-centered approach to treatment optimization. Through such endeavors, this innovative combination therapy may become an integral component of the standard care paradigm, ultimately enhancing outcomes and quality of life for patients with muscle-invasive bladder cancer.

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