Am J Cancer Res 2025;15(2):723-736
www.ajcr.us /ISSN:2156-6976/ajcr0162790

*Original Article*

# Radiotherapy can significantly improve survival outcomes in patients with muscle-invasive bladder cancer who are unsuitable for cystectomy or chemoradiotherapy

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Received December 19, 2024; Accepted February 8, 2025; Epub February 15, 2025; Published February 28, 2025

**Abstract:** Radical cystectomy and bladder preservation therapy are effective for muscle-invasive bladder cancer (MIBC); however, many patients over 70 are medically unfit for these options. For such patients, radiotherapy serves as a viable alternative. This study compares survival outcomes of radiotherapy versus supportive care in MIBC patients ineligible for cystectomy or bladder preservation with concurrent chemoradiotherapy. Using the Taiwan Cancer Registry and National Health Insurance Research Database (2011-2020), we identified patients with cT2-T4N0-1M0 urinary bladder urothelial carcinoma. Patients were excluded if they had undergone cystectomy or chemotherapy. Patients received either radiotherapy or supportive care, with endpoints of overall survival (OS) and cancer-specific survival (CSS) analyzed by Kaplan-Meier and multivariate Cox regression. Among 485 MIBC patients, 301 (62%) received radiotherapy, and 184 (38%) supportive care. After 13.93 months of median follow-up, radiotherapy significantly improved OS and CSS (P<0.001). Mortality rates were 26.9% for radiotherapy and 76.1% for supportive care at one year, and 59.5% vs. 94.0% at three years. OS and CSS benefits were confirmed for stages II-IV (adjusted hazard ratios: 5.47, 3.23, and 12.44, respectively), with T3, T4, N1, and chronic obstructive pulmonary disease (COPD) predicting worse OS. In conclusion, radiotherapy offers superior survival benefits compared to supportive care in MIBC patients who are unfit for cystectomy or chemoradiotherapy. These findings provide valuable insights for clinicians in making treatment decisions, particularly for elderly or medically unfit patients with early or locally advanced-stage MIBC.

**Keywords:** Muscle-invasive bladder cancer, radiotherapy, supportive care, survival, comorbidities

## Introduction

Bladder cancer is the second most common malignancy in the genitourinary system in the United States, with approximately 83,190 new cases and 16,840 deaths reported in 2024 [1]. Clinically, bladder cancer is categorized into three types: non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC), and metastatic disease, with about 25-30% of patients presenting with MIBC at diagnosis [2]. The incidence of bladder cancer increases with age, with a median age of 73 years at diagnosis [3].

The standard treatment for MIBC includes radical cystectomy, with or without neoadjuvant chemotherapy, or bladder preservation therapy. Bladder preservation typically involves maximal transurethral resection of the bladder tumor

https://doi.org/10.62347/XLPX5541

(TUR-BT) followed by concurrent chemoradiotherapy (CCRT) [4]. Both approaches achieve approximately 50-60% five-year overall survival rates [5-10]. However, cystectomy can significantly impact quality of life and may lead to perioperative complications, while chemotherapy often causes side effects such as cytopenia, nausea, vomiting, and diarrhea [11, 12]. For elderly patients or those with poor performance status or severe comorbidities, cystectomy or CCRT may not be feasible, resulting in a poorer prognosis [13]. Multiple treatment approaches will likely remain necessary for cancer management, with radiation therapy continuing to play a crucial role [14]. Potential mechanisms by which radiotherapy achieves local control in MIBC include tumor hypoxia modulation, DNA damage induction, immune system activation, and disruption of tumor vasculature [15, 16].

Advancements in radiotherapy techniques have shown promising results in achieving local control with minimal toxicity in MIBC patients [17]. Additionally, retrospective studies have underscored the effectiveness of radiotherapy in elderly patients with MIBC [18]. As a result, guidelines from the National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) recommend radiotherapy as a viable option for MIBC patients who are unsuitable for cystectomy or chemoradiotherapy due to comorbidities [19]. However, large comparative studies demonstrating the superiority of radiotherapy over supportive care in elderly or medically unfit MIBC patients remain lacking. To address this gap in evidence, this study aims to compare survival outcomes between radiotherapy and supportive care in MIBC patients who are ineligible for cystectomy or chemoradiotherapy.

## Materials and methods

### *Ethics approval and informed consent*

This study complied with all relevant guidelines and received approval from the Institutional Review Board of Chi-Mei Medical Center (IRB: CMFHR11205010), which waived the need for individual informed consent due to the anonymized nature of the data, free of personally identifiable information.

### *Data source and study cohort*

In this retrospective study, we analyzed data from the Taiwan Cancer Registry (TCR) to identify patients diagnosed with bladder cancer between January 1, 2011 and December 31, 2020. The TCR database, which covers approximately 97% of all cancer cases in Taiwan, ensures high accuracy in diagnosis and treatment coding, as validated by the National Health Insurance (NHI) institution [3]. Taiwan has been implementing national household registration since 1906. The information on birth, death, migration and marriage is registered with a unique citizenship ID number mandatorily and double-checked annually by household registration officers. Further, Taiwan's NHI provides health insurance for over 99% of the nation's residents and records the treatment of patients' comorbid conditions [20]. After 1985, the national death certificate database (DCD) started using all residents' unique citizenship ID number to link with TCR for prognosis investigation [21]. Based on DCD, the time interval of survival and cause of death in this study was determined, and the percentage of death certificate only (DCO) was 0.8% after 2011 [22].

Eligible participants were adults aged 18 years or older with histologically confirmed urothelial carcinoma of the urinary bladder. Tumor locations and histologic subtypes in the TCR database were classified using the *International Classification of Disease for Oncology, 3rd edition (ICD-O-3)*. Specifically, tumors located in the urinary bladder were identified using codes C67.0 through C67.9. Urothelial carcinoma, also known as transitional cell carcinoma, was identified with histologic code 8120 [23]. Patients were excluded if they had clinical stage T1 or M1, had undergone cystectomy or chemotherapy, or had missing survival data. Key demographic and clinicopathological data included age, gender, clinical T and N classification, Charlson Comorbidity Index (CCI), and type of comorbidities. Comorbidities were identified using *International Classification of Diseases, 9th Revision (ICD-9-CM)* codes prior to 2015 and *International Classification of Diseases, 10th Revision (ICD-10-CM)* codes thereafter.

We conducted a retrospective analysis to compare survival outcomes between patients receiving radiotherapy and those receiving supportive care alone. The radiotherapy group was defined as patients who received a cumulative radiation dose of more than 44 Gray (Gy). While the standard radiation dose for MIBC patients typically ranges from 60 to 66 Gy, there is no consensus on the optimal dose for elderly or frail patients. Previous studies have shown that elderly MIBC patients often receive radiation doses between 30 and 60 Gy [24, 25]. We defined the threshold at 44 Gy, as pelvic irradiation is typically delivered at 45-50.4 Gy in 25-28 fractions to regional lymphatics, allowing for a more tolerable yet potentially curative dose in elderly or frail populations. Patients who received only palliative radiotherapy for bone metastases or symptoms relief were categorized in the supportive care group. The primary endpoints were overall survival (OS) and cancer-specific survival (CSS). The follow-up period extended up to a maximum of three years, with patients who withdrew or were lost to follow-up being right-censored as of December 31, 2021.

*Statistical analysis*

The distribution of MIBC patients was presented as a number with frequency, and Pearson's chi-square test was used to assess the difference between patients receiving radiotherapy and those receiving supportive care. A Kaplan-Meier analysis was conducted to estimate OS and CSS, with survival information described in terms of median and quantiles. The log-rank test was used to compare the survival curves of the two treatment groups. Cox proportional regression models were used to compare the risk of mortality and cancer-specific mortality based on estimated hazard ratios (HRs) and 95% confidence intervals (CIs). The impact of comorbidities on OS and CSS between both groups was adjusted using multivariable Cox regression models. Additionally, stratified analyses were conducted to evaluate the consistency of results across all risk categories. Statistical significance was defined as $P<0.05$. All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute, Inc., Cary, NC, USA), and Kaplan-Meier curves were generated using STATA (version 15; Stata Corp., College Station, TX, USA).

## Results

*Patient characteristics*

The study flowchart is presented in **Figure 1**. Using the TCR database covering 2011 to 2020, we initially identified 12,969 patients diagnosed with bladder cancer. For analysis, we focused on patients with clinical stages T2-T4N0-1 and excluded those with distant metastasis. A total of 4,731 MIBC patients were diagnosed and met the inclusion criteria. After further excluding those who had undergone cystectomy or chemotherapy, 485 patients remained eligible for this study. Of these, 301 (62%) received radiotherapy, and 184 (38%) received supportive care. The demographic and clinicopathological characteristics of these patients are summarized in **Table 1**. In this cohort, the median age at diagnosis was 83 years, with 308 patients (63.5%) being male and 177 (36.5%) female. Clinical T classification showed that 249 cases (51.3%) were T2, 161 (33.2%) were T3, and 75 (15.5%) were T4. Clinical N classification indicated that 444 patients (91.5%) were N0, while 41 (8.5%) were N1. Patients in the radiotherapy group had a significantly lower prevalence of clinical stages III and IV compared to those receiving supportive care (P=0.001). Additionally, the type and severity of comorbidities, as well as personal habits, did not differ significantly between the two groups.

*Survival outcomes*

After a median follow-up of 13.93 months, patients treated with radiotherapy had significantly longer OS (median 23 months vs. 5.83 months; $P<0.001$) and CSS (median >36 months vs. 7.8 months; $P<0.001$) compared to those receiving supportive care (**Figure 2**). After adjustment for confounding factors, multivariable analysis confirmed that radiotherapy was significantly associated with improved OS and CSS. At one year, mortality rates were 26.91% in the radiotherapy group and 76.09% in the supportive care group (adjusted hazard ratio [aHR] 0.20; 95% CI, 0.15-0.27; $P<0.001$), and at three years, the rates were 59.47% and 94.02%, respectively (aHR 0.27; 95% CI, 0.22-0.34; $P<0.001$) (**Table 2**). Several variables and comorbid conditions, including gr-

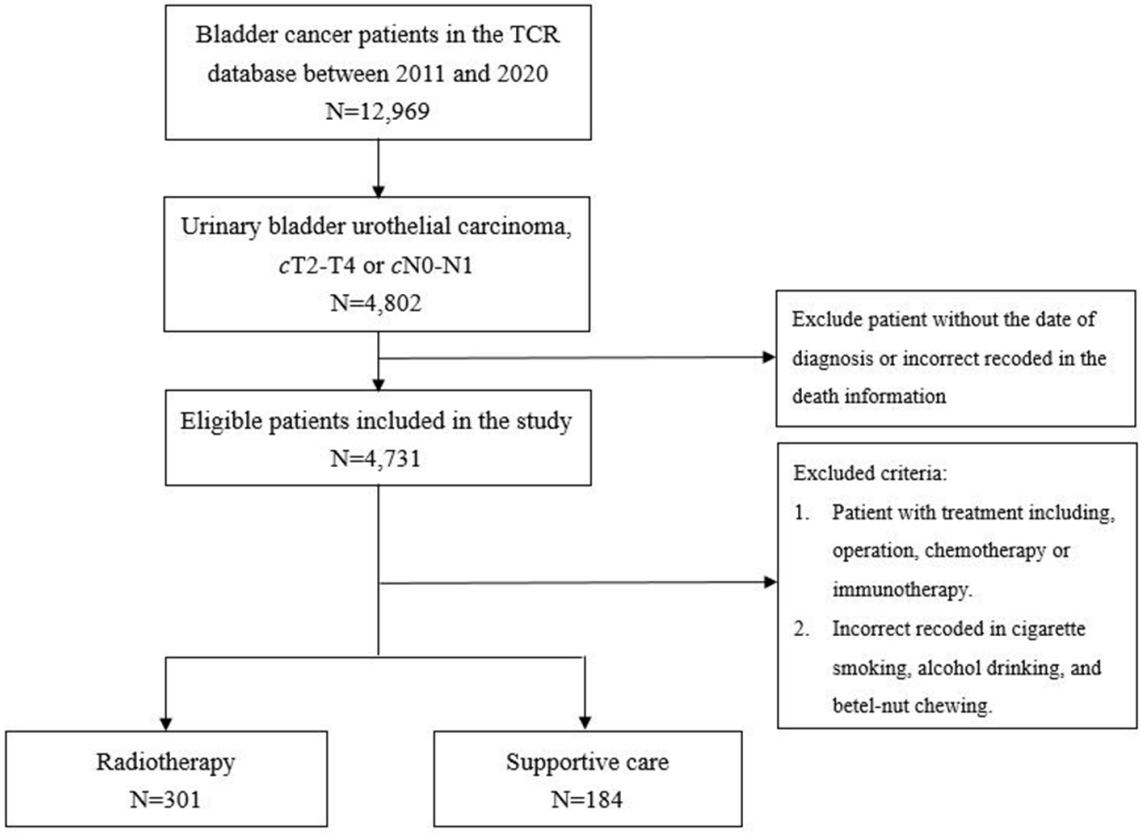



**Figure 1.** Flow chart of study population. Abbreviations: TCR, Taiwan cancer registry.

ade, clinical T classification, clinical N classification, and chronic obstructive pulmonary disease (COPD), were significantly correlated with survival outcomes (**Table 3**). Stratified analysis revealed that radiotherapy consistently improved OS and CSS across all risk categories defined by grade, clinical stage, and clinical T classification. As shown in **Figure 3**, radiotherapy continued to exhibit superior OS and CSS at both one and three years in patients with high grade (aHR 0.25; 95% CI, 0.20-0.33), clinical stage II (aHR 0.18; 95% CI, 0.13-0.26), stage III (aHR 0.28; 95% CI, 0.19-0.39), and stage IV (aHR 0.08; 95% CI, 0.02-0.30) diseases. These findings suggest that radiotherapy provides both immediate and sustained survival benefits for patients with early-stage as well as locally advanced MIBC.

## Discussion

In this retrospective study, we analyzed data from a nationwide cancer registry to show that radiotherapy was associated with significantly improved OS and CSS compared to supportive care among MIBC patients who were ineligible for curative cystectomy or chemoradiotherapy. Previous retrospective studies have emphasized the value of radiotherapy in achieving local control in MIBC, especially in elderly populations. For instance, a single-arm study by Aizawa et al. reported one-year OS, CSS, and progression-free survival (PFS) rates of 56.0%, 68.5%, and 40.0%, respectively [18]. To date, there have been no prospective studies and only limited retrospective studies comparing the efficacy of radiotherapy versus supportive care in elderly or medically unfit patients with MIBC. This study is one of the largest population-based analyses to date, providing valuable real-world evidence to address this critical clinical question.

The population in this study was representative of patients unable to tolerate major surgery or cytotoxic chemotherapy. Although prior research has explored the use of radiotherapy in elderly patients, definitions of “elderly” vary

**Table 1.** Baseline characteristics of muscle-invasive bladder cancer (MIBC) patients treated with radiotherapy and supportive care, N=485

| | MIBC patients, n (%) | | *P*-value |
|---|---|---|---|
| | Radiotherapy N=301 | Supportive care N=184 | |
| Age group, years | | | 0.632 |
| <65 | 21 (6.98) | 15 (8.15) | |
| ≥65 | 280 (93.02) | 169 (91.85) | |
| Sex | | | 0.021 |
| Male | 203 (67.44) | 105 (57.07) | |
| Female | 98 (32.56) | 79 (42.93) | |
| Grade | | | 0.001 |
| Low | 13 (4.32) | 7 (3.80) | |
| High | 275 (91.36) | 152 (82.61) | |
| Undifferentiated | 13 (4.32) | 25 (13.59) | |
| Clinical stage | | | 0.001 |
| II | 166 (55.15) | 70 (38.04) | |
| III | 114 (37.87) | 93 (50.54) | |
| IV | 21 (6.98) | 21 (11.41) | |
| cT classification | | | <0.001 |
| 2 | 173 (57.48) | 76 (41.30) | |
| 3 | 94 (31.23) | 67 (36.41) | |
| 4 | 34 (11.30) | 41 (22.28) | |
| cN classification | | | 0.247 |
| 0 | 279 (92.69) | 165 (89.67) | |
| 1 | 22 (7.31) | 19 (10.33) | |
| CCI score | | | 0.162 |
| 0 | 104 (34.55) | 54 (29.35) | |
| 1 | 70 (23.26) | 36 (19.57) | |
| ≥2 | 127 (42.19) | 94 (51.09) | |
| Smoking, yes | 91 (30.23) | 48 (26.09) | 0.327 |
| Drinking, yes | 38 (12.62) | 26 (14.13) | 0.635 |
| Comorbidities | | | |
| CKD | 50 (16.61) | 36 (19.57) | 0.410 |
| DM | 75 (24.92) | 53 (28.80) | 0.346 |
| HTN | 140 (46.51) | 84 (45.65) | 0.854 |
| CHF | 28 (9.30) | 20 (10.87) | 0.575 |
| COPD | 48 (15.95) | 21 (11.41) | 0.166 |

*P*-value was derived from Pearson's Chi-square test. Abbreviations: MIBC, muscle-invasive bladder cancer; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

widely across studies. For instance, Korpics et al. conducted a retrospective analysis using the National Cancer Database (NCDB) and found that patients aged 80 and older receiving CCRT had improved OS compared to those receiving radiotherapy alone [26]. In contrast, Carrion et al. found no significant difference in median OS between standard and palliative management among MIBC patients over 85 [27]. Standard therapies in that study included cystectomy, chemoradiotherapy, and radiotherapy alone. Other studies suggest that patients over 75 may experience higher post-treatment mortality rates following radical cystectomy or chemotherapy [28]. Patients with severe comorbidities may also be unsuitable for major surgery or cytotoxic chemotherapy. Our study specifically focused on patients ineligible for cystectomy or chemoradiotherapy, demonstrating that radiotherapy can provide favorable survival outcomes not only for elderly patients but also for those who are medically unfit. This analysis contributes valuable insights into treatment options for a subset of patients who face limited therapeutic alternatives due to advanced age or significant medical constraints.

Several prognostic factors - such as age, advanced disease stage, poor baseline performance status, tumor-associated carcinoma in situ, and comorbidities - have been identified as contributors to decreased survival [29-33]. Our analysis examined prognostic factors for survival across treatment groups, including age, gender, clinical stage, clinical T and N classification, and CCI scores. We also incorporated data from the NHIRD to evaluate the impact of comorbidities. With comprehensive variables and complete treatment records, we identified clinical T and N classification and COPD as significant predictors of OS. After adjusting for covariates, both mortality and cancer-specific mortality rates at one and three years were lower in the radiotherapy group than in the supportive care group, indicating that radiotherapy provides both immediate and sustained survival bene-

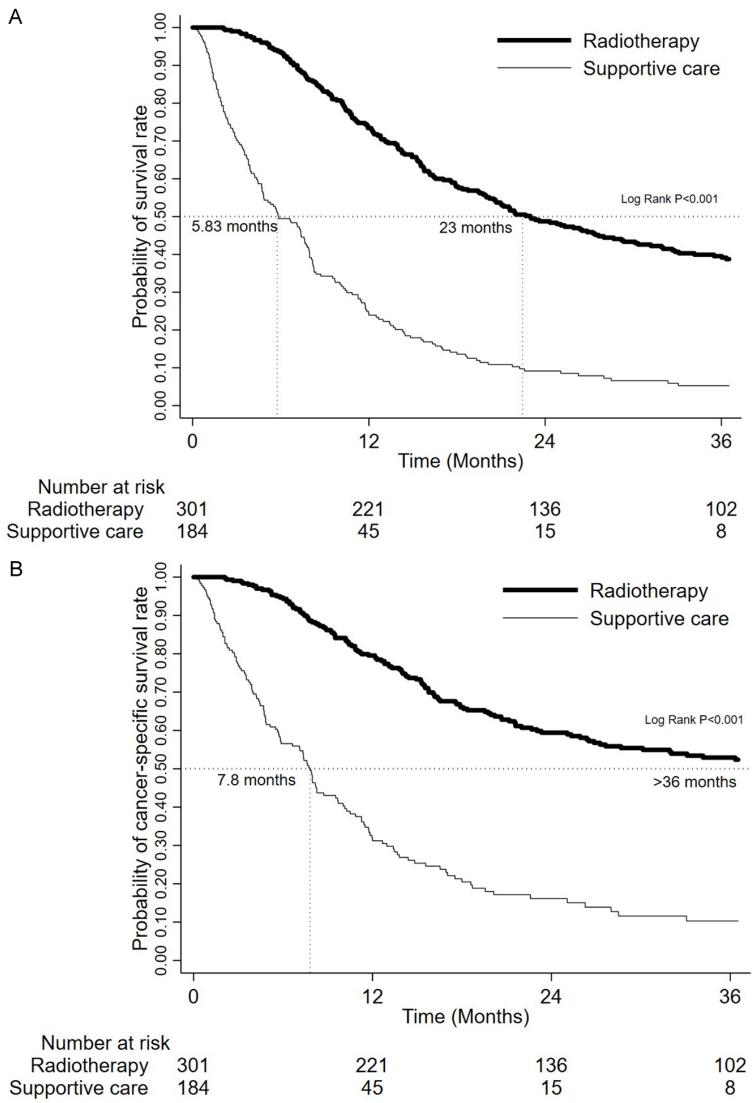



**Figure 2.** Kaplan-Meier plots of (A) overall survival, and (B) cancer-specific survival between radiotherapy and supportive care in muscle-invasive bladder cancer (MIBC) patients who were not suitable for curative cystectomy or chemoradiotherapy.

fits. To further clarify radiotherapy's impact, we performed a stratified analysis, which showed significant improvements in OS and CSS across all risk categories, including grade, clinical stage, and clinical T classification. This suggests that radiotherapy offers survival benefits in both early-stage and locally advanced MIBC. The potential explanation may be that radiotherapy could improve local control in MIBC patients by modulating tumor hypoxia, inducing DNA damage, activating the immune system, and disrupting tumor vasculature, ultimately leading to a greater survival benefit. Aligned with NCCN guidelines, radiotherapy is recommended for elderly or medically unfit individuals with clinical T2-4a or N1 MIBC, supporting the use of radiotherapy as a valuable option for those who are ineligible for more aggressive treatments.

The standard radiation dose for MIBC patients typically ranges from 60 to 66 Gy, yet there is no consensus on an optimal dose for elderly or frail patients. A study by the Italian Association of Radiotherapy and Clinical Oncology found that elderly patients often received palliative radiotherapy at a dose of 30 Gy in 10 fractions [25]. Similarly, Maebayashi et al., in a retrospective analysis, reported that patients aged 75 to 91 received radiation doses ranging from 45 to 60 Gy [24]. Based on these findings, we defined the radiotherapy group in this study as patients receiving a definitive radiation dose exceeding 44 Gy, which allowed for a potentially lower, more tolerable dose with curable intent in elderly or frail populations.

Most patients in our study received conformal radiotherapy, including intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) combining with image guide technique, now widely adopted for treating bladder cancer. IMRT or VMAT has shown favorable locoregional control rates while minimizing urinary and intestinal toxicity, suggesting that it is an effective and feasible treatment option for elderly or medically unfit patients with MIBC [34]. Advances in image-guided adaptive techniques have further improved the precision of radiotherapy for bladder cancer [35]. Furthermore, several innovative techniques for treating MIBC are currently being explored. Proton beam therapy, for

**Table 2.** The relative risk of mortality and cancer-specific mortality between radiotherapy and supportive care in muscle-invasive bladder cancer (MIBC) patients who were not suitable for cystectomy or chemoradiotherapy

| | MIBC patients, n (%) | | *P*-value | Mortality | Cancer-specific mortality |
|---|---|---|---|---|---|
| | Radiotherapy N=301 | Supportive care (Reference) N=184 | | Adjusted HR (95% CIs) | Adjusted HR (95% CIs) |
| Mortality 1 year | 81 (26.91) | 140 (76.09) | <0.001 | 0.20 (0.15-0.27) | 0.21 (0.15-0.29) |
| Time to death, year | | | | | |
| Median (Q1-Q3) | 0.64 (0.50-0.84) | 0.33 (0.16-0.63) | | | |
| Mortality 3 years | 179 (59.47) | 173 (94.02) | <0.001 | 0.27 (0.22-0.34) | 0.26 (0.20-0.34) |
| Time to death, year | | | | | |
| Median (Q1-Q3) | 1.07 (0.69-1.66) | 0.45 (0.19-0.89) | | | |

*P*-value was derived from Log rank test. The adjusted variables included age, sex, cancer status, and comorbidities. Abbreviations: MIBC, muscle-invasive bladder cancer; adjusted HR, adjusted hazard ratio.

**Table 3.** Prognostic factors of (A) mortality, and (B) cancer-specific mortality in muscle-invasive bladder cancer (MIBC) patients who were not suitable for cystectomy or chemoradiotherapy

(A)

| | 1-year | | 3-year | |
|---|---|---|---|---|
| | Adjusted HR (95% C.I.) | *P*-value | Adjusted HR (95% C.I.) | *P*-value |
| Treatment | | | | |
| Radiotherapy | 0.20 (0.15-0.27) | <.001 | 0.27 (0.22-0.34) | <.001 |
| Supportive care | Ref. | | Ref. | |
| Age group, years | | | | |
| <65 | Ref. | | Ref. | |
| ≥65 | 0.92 (0.52-1.64) | 0.783 | 0.98 (0.62-1.55) | 0.919 |
| Sex | | | | |
| Male | 1.00 (0.72-1.37) | 0.976 | 0.94 (0.73-1.21) | 0.612 |
| Female | Ref. | | Ref. | |
| Grade | | | | |
| Low | Ref. | | Ref. | |
| High | 1.80 (0.81-3.98) | 0.150 | 1.82 (1.01-3.31) | 0.048 |
| Undifferentiated | 3.28 (1.39-7.72) | 0.007 | 2.87 (1.47-5.61) | 0.002 |
| cT classification | | | | |
| 2 | Ref. | | Ref. | |
| 3 | 1.56 (1.13-2.16) | 0.007 | 1.41 (1.10-1.82) | 0.007 |
| 4 | 2.24 (1.58-3.18) | <.001 | 2.16 (1.61-2.90) | <.001 |
| cN classification | | | | |
| 0 | Ref. | | Ref. | |
| I | 1.80 (1.19-2.74) | 0.006 | 1.65 (1.15-2.37) | 0.006 |
| CCI score | | | | |
| 0 | Ref. | | Ref. | |
| 1 | 1.21 (0.78-1.87) | 0.406 | 1.11 (0.79-1.56) | 0.535 |
| ≥2 | 1.45 (0.96-2.18) | 0.076 | 1.34 (0.96-1.85) | 0.082 |
| Smoking, yes | 0.83 (0.56-1.22) | 0.338 | 0.89 (0.66-1.19) | 0.427 |
| Drinking, yes | 0.86 (0.54-1.39) | 0.546 | 0.85 (0.59-1.22) | 0.377 |

| | | | | |
|---|---|---|---|---|
| Comorbidities | | | | |
| CKD | 1.19 (0.80-1.75) | 0.394 | 1.09 (0.79-1.51) | 0.605 |
| DM | 1.20 (0.87-1.66) | 0.268 | 1.05 (0.81-1.37) | 0.712 |
| HTN | 0.84 (0.63-1.13) | 0.249 | 0.85 (0.67-1.06) | 0.151 |
| CHF | 1.06 (0.69-1.63) | 0.799 | 1.10 (0.77-1.56) | 0.604 |
| COPD | 1.98 (1.32-2.98) | 0.001 | 1.54 (1.10-2.15) | 0.013 |

(B)

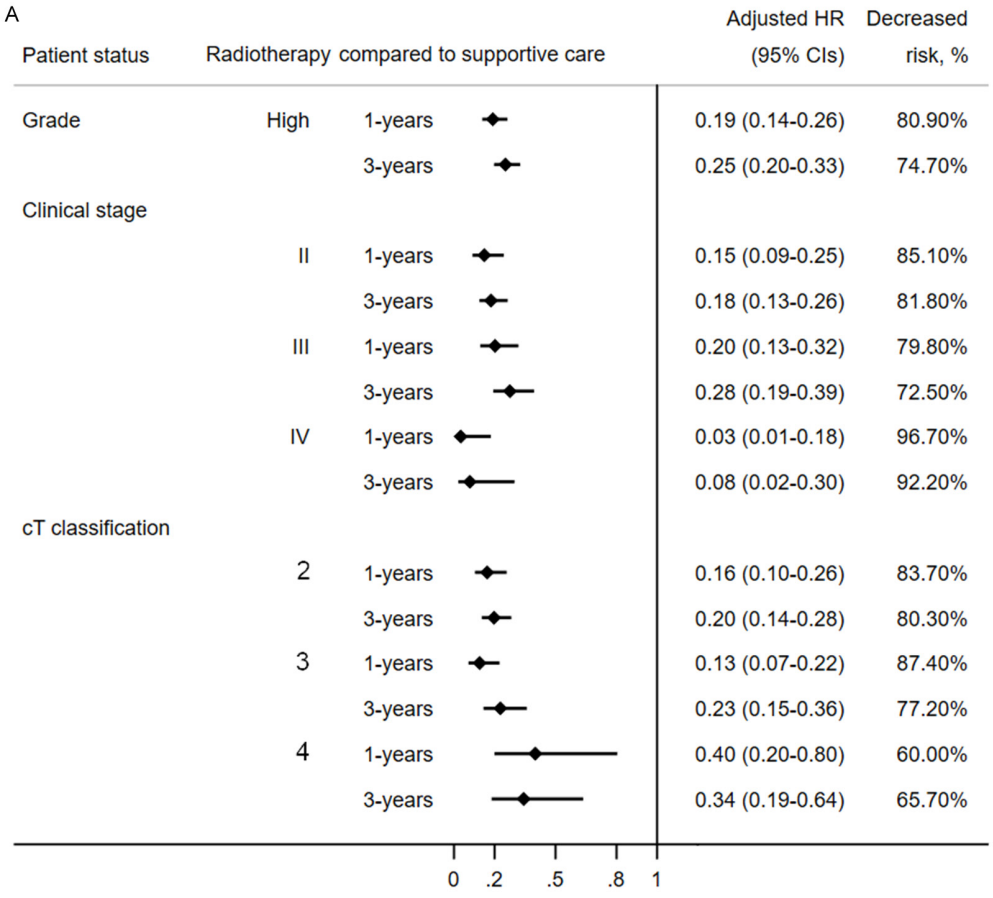
| | 1-year | | 3-years | |
|---|---|---|---|---|
| | Adjusted HR (95% C.I.) | *P*-value | Adjusted HR (95% C.I.) | *P*-value |
| Treatment | | | | |
| Radiotherapy | 0.21 (0.15-0.29) | <.001 | 0.26 (0.20-0.34) | <.001 |
| Supportive care | Ref. | | Ref. | |
| Age group, years | | | | |
| <65 | Ref. | | Ref. | |
| ≥65 | 0.77 (0.43-1.38) | 0.382 | 0.76 (0.47-1.22) | 0.250 |
| Sex | | | | |
| Male | 0.98 (0.69-1.40) | 0.912 | 0.97 (0.73-1.30) | 0.849 |
| Female | Ref. | | Ref. | |
| Grade | | | | |
| Low | Ref. | | Ref. | |
| High | 2.09 (0.82-5.29) | 0.122 | 1.95 (1.00-3.82) | 0.052 |
| Undifferentiated | 4.28 (1.60-11.49) | 0.004 | 3.06 (1.44-6.49) | 0.004 |
| cT classification | | | | |
| 2 | Ref. | | Ref. | |
| 3 | 1.53 (1.07-2.21) | 0.021 | 1.51 (1.13-2.02) | 0.005 |
| 4 | 2.20 (1.47-3.28) | <.001 | 2.14 (1.52-3.02) | <.001 |
| cN classification | | | | |
| 0 | Ref. | | Ref. | |
| I | 1.93 (1.23-3.02) | 0.004 | 1.77 (1.20-2.63) | 0.004 |
| CCI score | | | | |
| 0 | Ref. | | Ref. | |
| 1 | 1.43 (0.89-2.30) | 0.144 | 1.11 (0.76-1.64) | 0.586 |
| ≥2 | 1.44 (0.92-2.27) | 0.114 | 1.25 (0.87-1.81) | 0.234 |
| Smoking, yes | 0.72 (0.46-1.13) | 0.155 | 0.72 (0.51-1.03) | 0.068 |
| Drinking, yes | 0.98 (0.58-1.68) | 0.950 | 0.95 (0.62-1.44) | 0.801 |
| Comorbidities | | | | |
| CKD | 1.00 (0.62-1.59) | 0.989 | 0.95 (0.64-1.41) | 0.805 |
| DM | 1.20 (0.83-1.74) | 0.339 | 1.09 (0.79-1.49) | 0.602 |
| HTN | 0.70 (0.50-0.97) | 0.033 | 0.76 (0.58-0.99) | 0.042 |
| CHF | 1.00 (0.60-1.66) | 0.984 | 1.05 (0.68-1.62) | 0.823 |
| COPD | 1.30 (0.78-2.19) | 0.318 | 1.07 (0.68-1.66) | 0.780 |

Abbreviations: adjusted HR, adjusted hazard ratio; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease.

example, shows promising outcomes and is increasingly used for MIBC patients [36]. Studies also suggest that combining radiotherapy with hyperthermia is well-tolerated and effective, achieving high and durable local control rates. This combination therapy offers a promising option for elderly and frail MIBC patients who are unsuitable for surgery or CCRT [37, 38].

Recent advances in immunotherapy have shown promising clinical benefits in urothelial

A


Patient status
Radiotherapy compared to supportive care
Adjusted HR (95% CIs)
Decreased risk, %
Grade
High
1-years
0.19 (0.14-0.26)
80.90%
3-years
0.25 (0.20-0.33)
74.70%
Clinical stage
II
1-years
0.15 (0.09-0.25)
85.10%
3-years
0.18 (0.13-0.26)
81.80%
III
1-years
0.20 (0.13-0.32)
79.80%
3-years
0.28 (0.19-0.39)
72.50%
IV
1-years
0.03 (0.01-0.18)
96.70%
3-years
0.08 (0.02-0.30)
92.20%
cT classification
2
1-years
0.16 (0.10-0.26)
83.70%
3-years
0.20 (0.14-0.28)
80.30%
3
1-years
0.13 (0.07-0.22)
87.40%
3-years
0.23 (0.15-0.36)
77.20%
4
1-years
0.40 (0.20-0.80)
60.00%
3-years
0.34 (0.19-0.64)
65.70%
0 .2 .5 .8 1

B

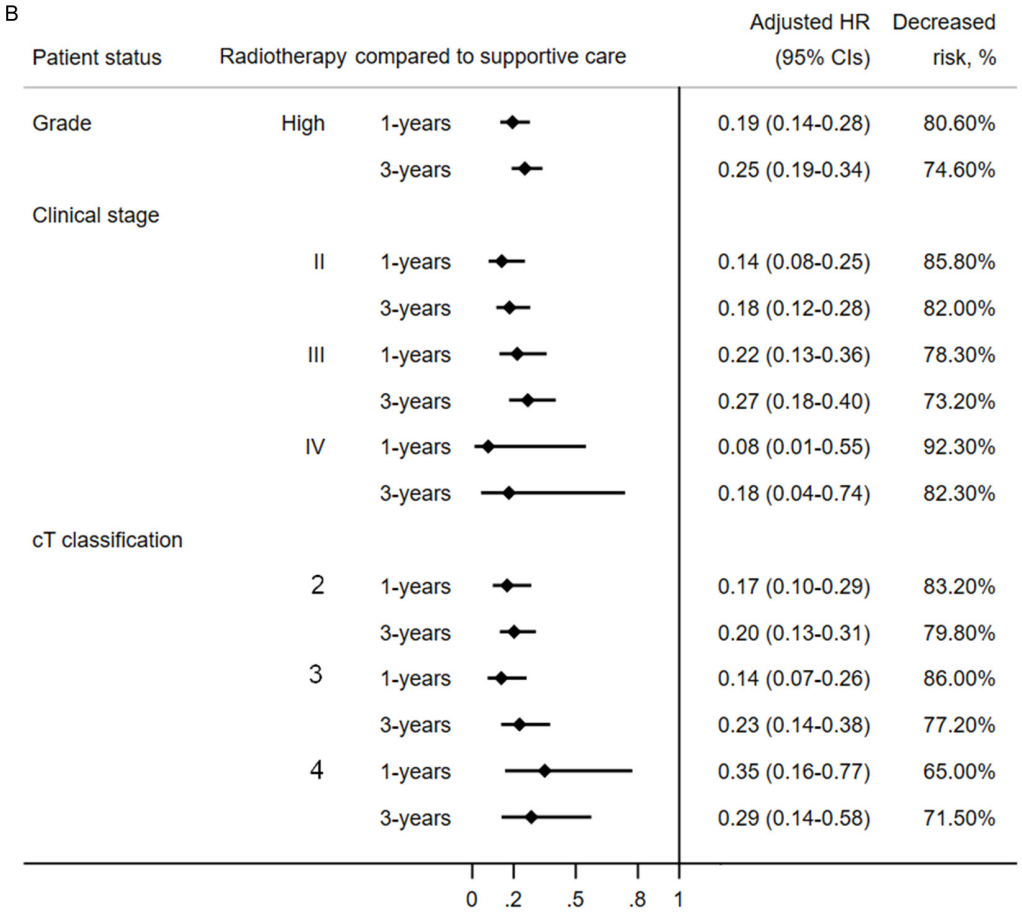

Patient status
Radiotherapy compared to supportive care
Adjusted HR (95% CIs)
Decreased risk, %
Grade
High
1-years
0.19 (0.14-0.28)
80.60%
3-years
0.25 (0.19-0.34)
74.60%
Clinical stage
II
1-years
0.14 (0.08-0.25)
85.80%
3-years
0.18 (0.12-0.28)
82.00%
III
1-years
0.22 (0.13-0.36)
78.30%
3-years
0.27 (0.18-0.40)
73.20%
IV
1-years
0.08 (0.01-0.55)
92.30%
3-years
0.18 (0.04-0.74)
82.30%
cT classification
2
1-years
0.17 (0.10-0.29)
83.20%
3-years
0.20 (0.13-0.31)
79.80%
3
1-years
0.14 (0.07-0.26)
86.00%
3-years
0.23 (0.14-0.38)
77.20%
4
1-years
0.35 (0.16-0.77)
65.00%
3-years
0.29 (0.14-0.58)
71.50%
0 .2 .5 .8 1

**Figure 3.** Stratified analysis of (A) mortality risk, and (B) cancer-specific mortality risk between radiotherapy and supportive care based on different clinicopathological features, including grade, clinical stage, and clinical T classification. The adjusted variables included age, sex, cancer status, and comorbidities. Abbreviations: adjusted HR, adjusted hazard ratio.

carcinoma [39, 40]. Studies indicate that adjuvant nivolumab or pembrolizumab significantly prolongs disease-free survival compared to observation alone in high-risk muscle-invasive urothelial carcinoma patients following radical surgery [41, 42]. Additionally, perioperative durvalumab combined with neoadjuvant chemotherapy has demonstrated superior overall survival compared to neoadjuvant chemotherapy alone for MIBC patients [43]. Radiotherapy has the potential to synergize with immunotherapy to improve outcomes in patients with MIBC [44]. Numerous preclinical and clinical studies have also highlighted the abscopal effect of radiotherapy when combined with immunotherapy, suggesting this combination as a potential treatment strategy for bladder cancer [44-47]. A phase III trial is currently underway to compare the efficacy of bladder preservation therapy using CCRT with pembrolizumab versus CCRT alone in MIBC patients (NCT04241185). Ongoing research into novel agents and techniques may further enhance treatment options and outcomes for MIBC patients who are ineligible for major surgery or cytotoxic chemotherapy.

MIBC exhibits biological diversity and can be categorized into basal type, luminal type, and p53-like MIBC based on gene expression patterns [48]. Several molecular biomarkers have been recognized as prognostic or predictive indicators for chemoradiotherapy in MIBC [49]. Inoue et al. identified that overexpression of ERBB2 is relevant to chemoradiotherapy resistance in MIBC patients treated with bladder preservation therapy [50]. Efstathiou et al. utilized gene expression profiling and discovered that higher immune infiltration is associated with improved survival outcomes following chemoradiotherapy in MIBC [51]. Magliocco et al. analyzed MIBC patients pooled from six prospective Radiation Therapy Oncology Group (RTOG) studies and found that higher levels of MRE11 were associated with lower mortality rates after chemoradiotherapy [52]. These biomarkers could help identify subgroups of MIBC patients who more likely to benefit from radiotherapy, thereby assisting physicians in selecting the most appropriate treatment options for elderly or medically unfit patients.

This study has a few limitations. First, the accuracy of data collection and selection bias inherent to its retrospective design could be a concern. Therefore, the NHI database was used to minimize the impact of missing records. Stratified analyses based on tumor grade, clinical stage, and clinical T classification, was be applied to ensure that patient had a similar grade or advanced-stage MIBC under radiotherapy or supportive care. Second, several prognostic factors were not available in the TCR database, including multifocality, concomitant carcinoma in situ, and hydronephrosis. Nevertheless, age, gender, clinical stage, clinical T and N classification, and CCI scores were incorporated into the analysis as the significant prognostic factors influencing survival. To determine the relative risk of OS and CSS between treatments, these potential risk factors were adjusted using multivariable Cox regression models. Third, data on local control rates, adverse effects, and quality of life were also absent, constraining our ability to evaluate real-world safety outcomes. Finally, follow-up periods were relatively short. Notably, the 3-year mortality rate for the supportive care group was 94.02%, indicating that most patients in this group passed away within three years.

## Conclusion

This study demonstrated that radiotherapy provides superior survival outcomes compared to supportive care for MIBC patients who are ineligible for cystectomy or chemoradiotherapy. Radiotherapy should be considered a feasible and effective treatment option for MIBC, especially in elderly or medically unfit patients. Future research should prioritize the evaluation of novel agents and techniques to improve treatment options and further enhance survival outcomes in these vulnerable patient populations.

## Acknowledgements

We are grateful to Health Data Science Center, National Cheng Kung University Hospital for providing administrative and technical support.

## Disclosure of conflict of interest

None.

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