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Impact of HER2 Expression on the Prognosis of Muscle-Invasive Bladder Cancer Patients Treated with Bladder-Preservation Comprehensive Therapy

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Abstract

Background HER2 expression has been confirmed to be associated with bladder cancer aggressiveness. Anti-HER2 RC48-ADC is approved in China for the treatment of patients with advanced urothelial carcinoma with failed chemotherapy who are HER2 positive (IHC 2 + or 3 +). The discovery of HER2 positivity in urothelial carcinoma and the development of anti-HER2 drugs have brought new hope for bladder preservation treatment in MIBC.

Objective To investigate HER2 expression in MIBC patients and its correlations with clinical characteristics, to analyze the impact of HER2 expression on the prognosis of MIBC patients administered bladder-preservation comprehensive therapy, and to explore the efficacy and safety of RC48-ADC in MIBC patients administered bladder-preservation comprehensive therapy.

Methods We retrospectively collected information on MIBC patients. All 217 patients underwent cTURBT, of whom 175 received GC chemotherapy, while the remaining 42, due to intolerance to GC chemotherapy and HER2 positivity (IHC 2 + or 3 +), received RC48-ADC treatment. Of the 175 patients administered cTURBT combined with GC chemotherapy, 92 and 83 were HER2-negative and HER2-positive, respectively. Recurrence-free survival (RFS) and overall survival (OS) in HER2-negative and HER2-positive patients were compared to analyze the correlation between HER2 expression and prognosis. RFS and OS in the 83 HER2-positive patients administered cTURBT combined with GC chemotherapy and the 42 HER2-positive patients administered cTURBT combined with RC48-ADC were compared to analyze the differences in prognosis between the two treatment methods. The adverse reactions of GC and RC48-ADC were also compared.

Results Among the 217 included patients, 125 (57.6%) were HER2 positive (IHC 2 + or 3 +). HER2 positivity was significantly associated with tumor size, multifocality, pathological grade, tumor stage, and pelvic lymph node metastasis ($P < 0.05$). Totally 175 patients underwent cTURBT combined with GC chemotherapy, including 92 HER2-negative and 83 HER2-positive cases. There were no significant differences in gender, age, smoking status, tumor location, and ECOG score between the two groups ($P > 0.05$), but the proportions of patients with tumors > 3 cm, multifocal tumors, T3 stage, high-grade tumors, and pelvic lymph node metastasis were higher in the HER2-positive group versus the HER2-negative group ($P < 0.05$). Tumor recurrence rate in the 83 HER2-positive patients was 67.5%, with a median RFS of 19.0 months (95% CI: 10.3–27.7). Totally 22 deaths occurred during the follow-up period,

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with a median OS of 56.0 months (95% CI: 45.7–66.3). In the 92 HER2-negative patients, the tumor recurrence rate was 56.5%, with a median RFS of 36.0 months (95% CI: 26.1–45.9); 4 deaths occurred during the follow-up period, with the median OS not reached. After cTURBT, of the 125 HER2-positive patients examined, 83 were included in the GC treatment group versus 42 in the RC48-ADC group. There were no differences in gender, age, smoking status, tumor location, tumor size, multifocality, clinical T stage, pathological grade, pelvic lymph node metastasis, and ECOG score between the two groups ($P > 0.05$). In the GC group, 56 recurrences (67.5%) were detected during the follow-up period, with a median RFS of 19.0 months (95% CI: 10.3–27.7); meanwhile, 22 deaths (52.4%) occurred, with a median OS of 56.0 months (95% CI: 45.7–66.3). In the RC48-ADC group, 15 recurrences (35.7%) were recorded during the follow-up period, with the median RFS not reached; there were 2 deaths (4.8%), with the median OS not reached. The incidence rates of any-grade and grade ≥ 3 adverse reactions were both lower in the RC48-ADC group than in the GC treatment group.

Conclusions This study confirms that cTURBT combined with RC48-ADC treatment for HER2-positive MIBC is superior to combined GC treatment in terms of RFS and OS, representing an effective treatment regimen for bladder preservation in MIBC patients.

Keywords HER2, Muscle-invasive bladder cancer, Prognosis, RC48-ADC, Chemotherapy

Background

The standard treatment option for muscle-invasive bladder cancer (MIBC) is radical cystectomy (RC) combined with pelvic lymph node dissection following neoadjuvant chemotherapy [1], which is highly invasive and associated with a high incidence of perioperative complications [2]. Patients who undergo this procedure often have to carry a urinary bag for life, which reduces the quality of life. In recent years, cancer treatment has shifted towards balancing survival and quality of life, making bladder-preservation comprehensive therapy an important treatment method for MIBC [3].

HER2 is a member of the human epidermal growth factor receptor family, and the rate of HER2 overexpression in urothelial carcinoma (UC) ranges from 24.1% to 61.1% [4–6]. A previous study showed that compared with non-muscle-invasive bladder cancer (NMIBC), MIBC and metastatic bladder cancer have significantly increased HER2 expression levels [7]. Therefore, HER2 expression may be associated with bladder cancer aggressiveness [8]. In recent years, anti-HER2 therapy has achieved great success in the treatment of breast and gastric cancers [9, 10]. Anti-HER2 drugs are currently being examined for the treatment of urothelial carcinoma. Clinical studies have shown that new small-molecule antibody–drug conjugates targeting HER2, including DV and RC48-ADC, have conferred survival benefits in second-line treatment of advanced urothelial carcinoma [11, 12]. Currently, RC48-ADC is approved in China for the treatment of patients with advanced urothelial carcinoma with failed chemotherapy who are HER2 positive (IHC 2 + or 3 +) [13]. The present study aimed to investigate HER2 expression in MIBC patients and its correlations with clinical characteristics, to analyze the impact of HER2 expression on the prognosis of MIBC patients administered bladder-preservation comprehensive therapy, and to explore the efficacy and safety of RC48-ADC in MIBC patients administered bladder-preservation comprehensive therapy.

Methods

Study subjects

We retrospectively collected information on MIBC patients treated in Tianjin Union Medical Center from January 2019 to January 2022.

Inclusion criteria were: (1) MIBC cases with stages T2 to T3, with pathological biopsy confirming urothelial carcinoma; (2) maximal transurethral resection of bladder tumor (cTURBT) and postoperative intravenous chemotherapy with gemcitabine combined with cisplatin (GC) or RC48-ADC, including 6 cycles for the postoperative GC chemotherapy or 6 cycles for RC48-ADC treatment.

Exclusion criteria were: (1) MIBC with distant metastasis; (2) completion of less than 6 cycles of postoperative GC chemotherapy or RC48-ADC; (3) incomplete follow-up information.

A total of 217 eligible MIBC patients were included in this study. Of these patients, 112 refused RC and actively requested bladder-preservation comprehensive therapy, while 105 were unable to tolerate RC due to old age, severe cardiopulmonary or cerebral diseases, or coagulation dysfunction. Patients and their families provided signed informed consent. All patients underwent preoperative urological ultrasound, abdominal CT, CTU, pelvic MRI, cystoscopy, and tissue biopsy to confirm the diagnosis and to determine the clinical stage and pathological grade.

Treatment method

The research roadmap of bladder-preservation comprehensive treatment is shown in Fig. 1. All 217 patients underwent cTURBT, of whom 175 received GC chemotherapy, while the remaining 42, due to intolerance to GC chemotherapy and HER2 positivity (IHC 2+or 3+), received RC48-ADC treatment. The clinicopathological characteristics and survival data collected included gender, age, smoking history, primary tumor site, tumor size, single or multiple, clinical stage, pathological grade, pelvic lymph node metastasis, HER2 expression levels, ECOG score, treatment status, and follow-up of patient recurrence status and survival time. During the follow-up period, B-mode ultrasound was performed every 3 months for the first year; pelvic MRI and cystoscopy were carried out every 3 to 6 months and after 24 months postoperatively; and B-mode ultrasound, pelvic MRI, and cystoscopy were conducted every 6 months. This study was approved by the Ethics Committee of Tianjin People's Hospital.

In cTURBT, resection of grossly visible tumors was performed, and patients with T3 stage disease underwent resection to visible extravesical fat. Electrocoagulation of the bladder mucosa was performed within 1 cm around the tumor base. In GC chemotherapy, patients received intravenous chemotherapy with the GC regimen one week postoperatively, with each 21 days constituting one chemotherapy cycle, for a total of six cycles. RC48-ADC was administered at a dose of 2 mg/kg, once every two weeks, for a total of six administrations.

Detection of HER2 expression

All bladder tumor tissue specimens from patients were assessed for HER2 expression by immunohistochemical staining (IHC). At least two experienced pathologists evaluated HER2 expression per the 2018 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines. Immunohistochemical staining of HER2 expression levels at 0, 1+, 2+, and 3+is shown in Fig. 2. HER2 expression at 2+or 3+was defined as HER2 positive, while 0 or 1+was defined as HER2 negative. The rate of HER2 positivity and its correlations with clinical characteristics were analyzed.

Treatment prognosis and adverse reaction evaluation

Of the 175 patients administered cTURBT combined with GC chemotherapy for bladder-preservation comprehensive treatment, 92 and 83 were HER2-negative and HER2-positive, respectively. Recurrence-free survival (RFS) and overall survival (OS) in HER2-negative and HER2-positive patients were compared to analyze the correlation between HER2 expression and prognosis after bladder-preservation comprehensive treatment.

RFS and OS in the 83 HER2-positive patients administered cTURBT combined with GC chemotherapy and the 42 HER2-positive patients administered cTURBT combined with RC48-ADC chemotherapy were compared to analyze the differences in prognosis between the two treatment methods; the adverse reactions of both chemotherapy methods were also compared. Adverse reactions after chemotherapy were evaluated per the grading standards set by the World Health Organization [14].

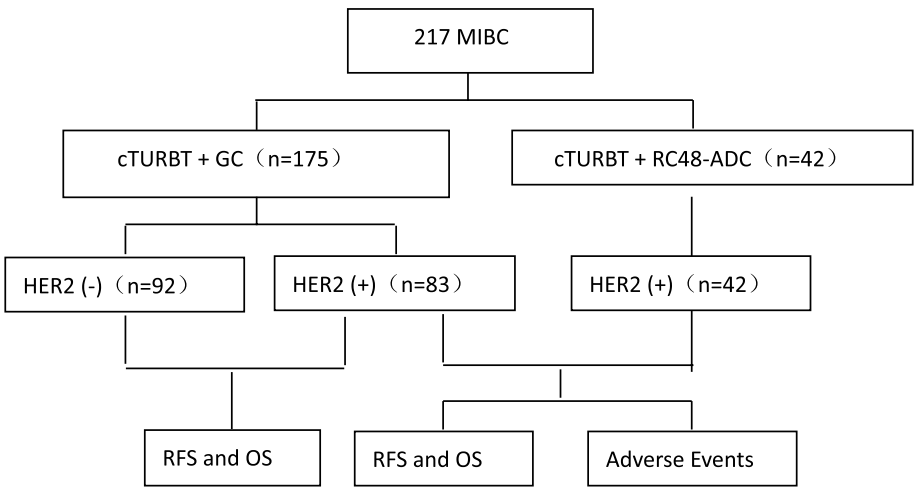

Fig. 1 Research Roadmap. MIBC, muscle-invasive bladder cancer; cTURBT, maximal transurethral resection of bladder tumor; GC, intravenous chemotherapy of gemcitabine combined with cisplatin; RFS, recurrence-free survival; OS, overall survival

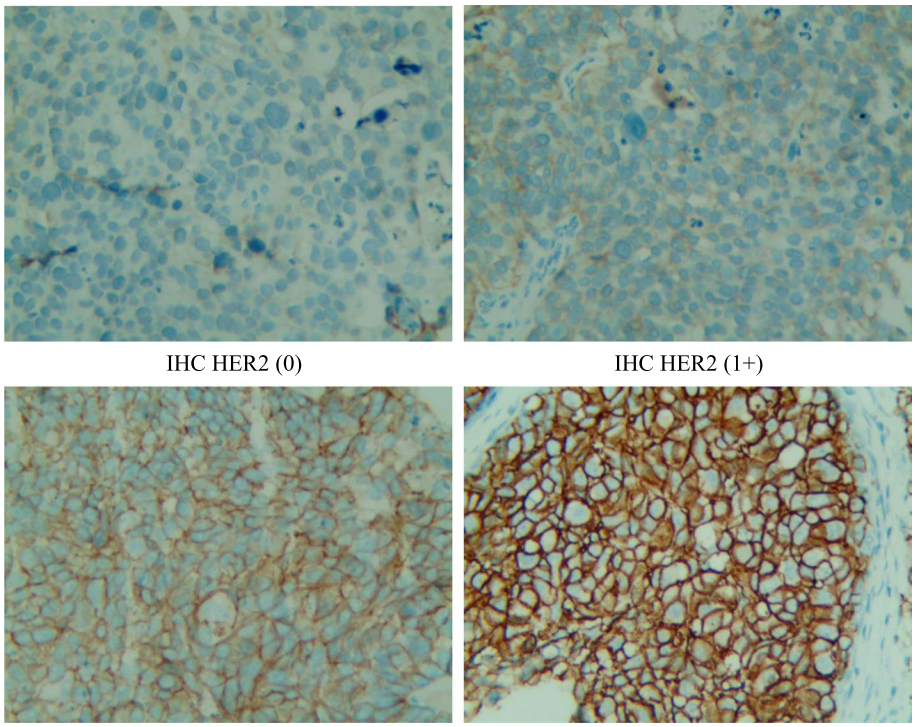

Fig. 2 Immunohistochemical staining of HER2 expression levels at 0, 1 +, 2 +, and 3 +

Statistical analysis

Count data with normal distribution were represented by mean ± standard deviation compared by the t-test or analysis of variance. Categorical variables were represented by frequency and compared by the chi-square test or Fisher's exact test. The Kaplan–Meier method was used to analyze RFS and OS, with $P < 0.05$ indicating a statistically significant difference. Statistical analysis was performed with the SPSS software (SPSS Inc., Chicago, Illinois) version 22.0.

Results

Baseline characteristics

The baseline characteristics of the 217 MIBC patients included in this study are shown in Table 1. There were 173 males (79.7%) and 44 females (20.3%), indicating a male-to-female ratio of 4:1. The average patient age was 72 years (40–85 years). High-grade urothelial carcinoma was detected in 208 cases (95.9%). Pelvic lymph node metastasis occurred in 29 patients (13.4%), of whom 23 were HER2 positive, accounting for 79.3% of patients with pelvic lymph node metastasis.

Correlations between HER2 expression levels in MIBC patients and clinical characteristics

Among the 217 included patients, 125 (57.6%) were HER2 positive (IHC 2 + or 3 +). No differences in HER2 positivity were found based on gender, age, smoking status, and tumor location ($P > 0.05$). However, HER2 positivity was significantly associated with tumor size, multifocality, pathological grade, tumor stage, and pelvic lymph node metastasis ($P < 0.05$) (Table 1).

Prognosis analysis

Totally 175 patients underwent cTURBT combined with GC chemotherapy for bladder-preservation comprehensive treatment, including 92 HER2-negative and 83 HER2-positive cases. There were no significant differences in gender, age, smoking status, tumor location, and ECOG score between the two groups ($P > 0.05$), but the proportions of patients with tumors > 3 cm, multifocal tumors, T3 stage, high-grade tumors, and pelvic lymph node metastasis were higher in the HER2-positive group versus the HER2-negative group ($P < 0.05$). Tumor recurrence rate in the 83 HER2-positive patients was 67.5%, with a median RFS of 19.0 months (95% CI: 10.3–27.7).

Table 1 Baseline characteristics and HER2 positivity of patients with MIBC

HER2 IHC expression N (%)	Total 217(100%)	Negative (0/1 +) 92(42.4%)	Positive (2 + /3 +) 125(57.6%)	*P*
Gender				0.572
Male	173(79.7%)	75(34.6%)	98(45.2%)	
Female	44(20.3%)	17(7.8%)	27(12.4%)	
Tumor size (cm)				< 0.001
≤ 3	125(57.6%)	73(33.6%)	52(24.0%)	
> 3	92(42.4%)	19(8.8%)	73(33.6%)	
Single or multiple				< 0.001
Single	130(59.9%)	74(34.1%)	56(25.8%)	
Multiple	87(40.1%)	18(8.3%)	69(31.8%)	
Pathological grades				< 0.001
Low grade	73(33.6%)	44(20.3%)	29(13.4%)	
High grade	144(66.4%)	48(22.1%)	96(44.2%)	
Clinical stages				< 0.001
T2	117(53.9%)	69(31.8%)	48(22.1%)	
T3	100(46.1%)	23(10.6%)	77(35.5%)	
Pelvic lymph nodes				0.011
Yes	29(13.4%)	6(2.8%)	23(10.6%)	
No	188(86.6%)	86(39.6%)	102(47.0%)	

Totally 22 deaths occurred during the follow-up period, with a median OS of 56.0 months (95% CI: 45.7–66.3). In the 92 HER2-negative patients, the tumor recurrence rate was 56.5%, with a median RFS of 36.0 months (95% CI: 26.1–45.9); 4 deaths occurred during the follow-up period, with the median OS not reached (Table 2). Recurrence-free and overall survival curves for HER2-negative and HER2-positive patients are shown in Fig. 3A and B, with HER2-negative patients having better RFS and OS benefits.

RC48-ADC showed better RFS and OS benefits compared with GC

After cTURBT, of the 125 HER2-positive patients examined, 83 were included in the GC treatment group versus 42 in the RC48-ADC chemotherapy group. There were no differences in gender, age, smoking status, tumor location, tumor size, multifocality, clinical T stage, pathological grade, pelvic lymph node metastasis, and ECOG score between the two groups ($P > 0.05$) (Table 3). In the GC group, 56 recurrences (67.5%) were detected during the follow-up period, with a median RFS of 19.0 months (95% CI: 10.3–27.7); meanwhile, 22 deaths (52.4%) occurred, with a median OS of 56.0 months (95% CI: 45.7–66.3). In the RC48-ADC group, 15 recurrences (35.7%) were recorded during the follow-up period, with the median RFS not reached; there were 2 deaths (4.8%), with the median OS not reached (Table 3). Survival curve analysis showed that the RC48 group had better RFS and OS benefits compared with the GC group (Fig. 4).

In terms of adverse reactions, the incidence of any-grade adverse events in the GC group was 92.8%, with grade ≥ 3 adverse events accounting for 27.7%. In the RC48-ADC group, the incidence of any-grade adverse events was 66.7%, with grade ≥ 3 adverse events accounting for 9.5% (Table 4). Common adverse reactions in the GC treatment group included gastrointestinal reaction (80.7%), fatigue (61.4%) and anemia (49.4%), versus liver function abnormalities (47.6%), alopecia (33.3%), fatigue (26.2%) and anemia (26.2%) in the RC48-ADC treatment group. The incidence rates of any-grade and grade ≥ 3 adverse reactions were both lower in the RC48-ADC group than in the GC treatment group.

Discussion

Currently, the triple therapy (TMT) of cTURBT combined with chemotherapy and radiotherapy is the recommended treatment option for bladder preservation [1, 15]. Some MIBC patients, due to advanced age or multiple comorbidities, cannot tolerate chemoradiotherapy, making the development of better bladder preservation treatment schemes a clinical focus. The discovery of HER2 positivity in urothelial carcinoma and the development of anti-HER2 drugs have brought new hope for bladder preservation treatment in MIBC [16].

A meta-analysis found that HER2 overexpression in 1398 bladder cancer patients is correlated with carcinoma

Table 2 Clinical data and correlation between HER2 expression levels and prognosis in the GC treatment group

HER2 IHC expression N (%)	Total 175(100%)	Negative (0/1 +) 92(52.6%)	Positive (2 +/3 +) 83(47.4%)	*P*
Gender				0.260
Male	139(79.4%)	75(42.9%)	64(36.6%)	
Female	36(20.6%)	17(9.7%)	19(10.9%)	
Tumor size (cm)				< 0.001
≤ 3	108(61.7%)	73(41.7%)	35(20.0%)	
> 3	67(38.3%)	19(10.9%)	48(27.4%)	
Single or multiple				0.042
Single	114(65.1%)	74(42.3%)	40(22.9%)	
Multiple	61(34.9%)	18(10.3%)	43(24.6%)	
Clinical stages				0.001
T2	98(56.0%)	69(39.4%)	29(16.6%)	
T3	77(44.0%)	23(13.1%)	54(30.9%)	
Pathological grading				0.002
Low grade	65(37.1%)	44(25.1%)	21(12.0%)	
High grade	110(62.9%)	48(27.4%)	62(35.4%)	
Pelvic lymph nodes				0.019
Yes	21(12.0%)	6(3.4%)	15(8.6%)	
No	154(88.0%)	86(49.1%)	68(38.9%)	
ECOG PS				0.303
0	117(66.9%)	57(32.6%)	60(34.3%)	
1–2	49(28.0%)	17(9.7%)	22(12.6%)	
3–4	9(5.1%)	8(4.6%)	1(0.6%)	
Recurrence				0.007
Yes	108(61.7%)	52(29.7%)	56(32.0%)	
No	67(38.3%)	40(22.9%)	27(15.4%)	
Median recurrence-free Survival time (95% CI)	28.0(21.2–34.8)	36.0(26.1–45.9)	19.0(10.3–27.7)	0.021
Death				< 0.001
Yes	26(14.9%)	4(2.3%)	22(12.6%)	
No	149(85.1%)	88(50.3%)	61(34.9%)	
Median overall survival time (95% CI)	-	-	56.0(45.7–66.3)	< 0.001

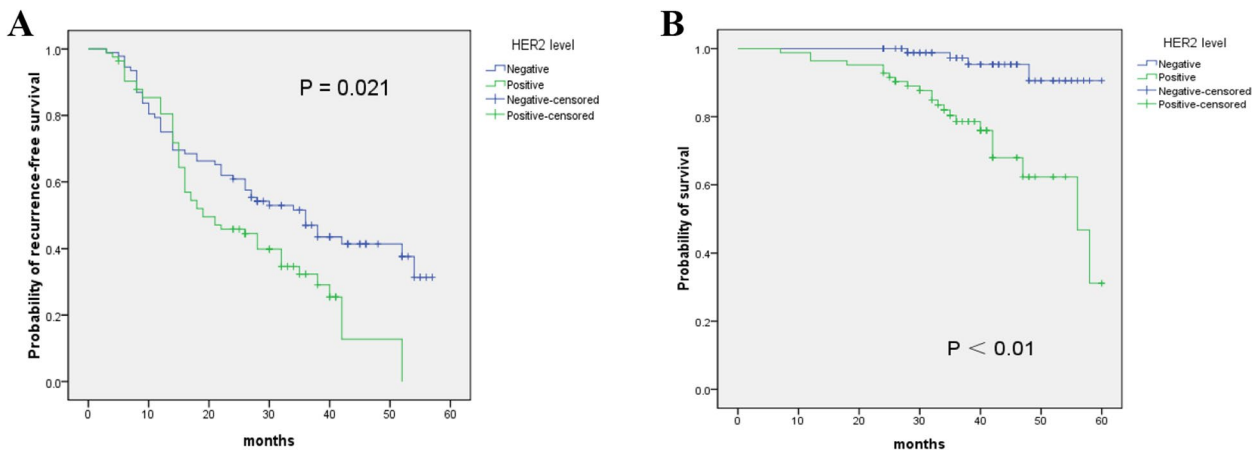

Fig. 3 Kaplan–Meier analyses of RFS and OS based on HER2 positivity. **A** Recurrence-free survival (RFS). **B** Overall survival (OS)

Table 3 Clinical data and prognosis analysis of HER2-positive patients in the GC and RC48 groups

N (%)	Total 125(100%)	TURBT + GC 83(66.4%)	TURBT + RC48-ADC 42(33.6%)	*P*
Gender				0.622
Male	98(78.4%)	64(51.2%)	34(27.2%)	
Female	27(21.6%)	19(15.2%)	8(6.4%)	
Tumor size (cm)				0.856
≤ 3	52(41.6%)	35(28.0%)	17(13.6%)	
> 3	73(58.4%)	48(38.4%)	25(20.0%)	
Single or multiple				0.284
Single	56(44.8%)	40(32.0%)	16(12.8%)	
Multiple	69(55.2%)	43(34.4%)	26(20.8%)	
Clinical stages				0.068
T2	48(38.4%)	29(23.2%)	19(15.2%)	
T3	77(61.6%)	54(43.2%)	23(18.4%)	
Pathological grade				0.434
Low grade	29(23.2%)	21(16.8%)	8(6.4%)	
High grade	96(76.8%)	62(49.6%)	34(27.2%)	
Pelvic lymph nodes				0.537
Yes	23(18.4%)	15(12.0%)	8(6.4%)	
No	102(81.6%)	68(54.4%)	34(27.2%)	
ECOG PS				0.615
0	86(68.8%)	60(48.0%)	26(20.8%)	
1–2	36(28.8%)	22(17.6%)	14(11.2%)	
3–4	3(2.4%)	1(0.8%)	2(1.6%)	
Recurrence				0.001
Yes	71(56.8%)	56(44.8%)	15(12.0%)	
No	54(43.2%)	27(21.6%)	27(21.6%)	
Median recurrence-free survival time (95% CI)	-	19.0(10.3–27.7)	-	< 0.001
Death				0.004
Yes	24(19.2%)	22(17.6%)	2(1.6%)	
No	101(80.8%)	61(48.8%)	40(32.0%)	
Median overall survival time (95% CI)	-	56.0(45.7–66.3)	-	< 0.001

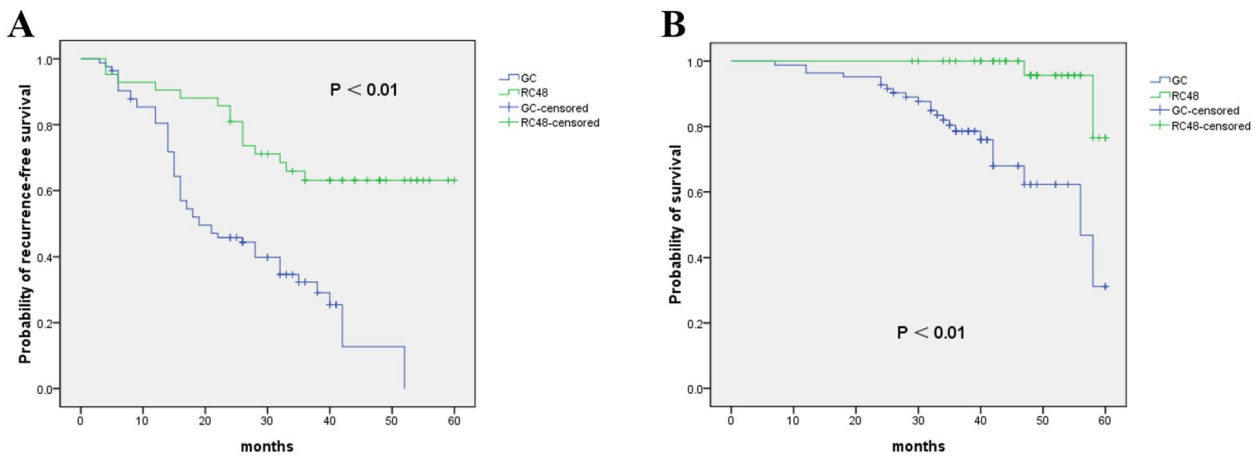

Fig. 4 Kaplan–Meier analyses of RFS and OS for the GC and RC48-ADC groups. **A** Recurrence-free survival (RFS). **B** Overall survival (OS)

Table 4 Treatment-related adverse events of GC and RC48-ADC

Adverse event	Any grade			Grade ≥ 3		
	GC(*N* = 83)	RC48(*N* = 42)	*P*	GC(*N* = 83)	RC48(*N* = 42)	*P*
	Number of patients (percent)					
Any adverse event	77 (92.8%)	28(66.7%)	< 0.001	23(27.7%)	4(9.5%)	0.020
Peripheral sensory neuropathy	9 (10.8%)	7(16.7%)	0.357	0	0	-
Alopecia	6(7.2%)	14(33.3%)	< 0.001	0	0	-
Skin reactions	4(4.8%)	2(4.8%)	1.000	2(2.4%)	0	0.550
Fever	3(3.6%)	1(2.4%)	1.000	0	0	-
Fatigue	51(61.4%)	11(26.2%)	< 0.001	9(10.8%)	0	0.028
Gastrointestinal reaction	67(80.7%)	8(19.0%)	< 0.001	12(14.5%)	1(2.4%)	0.037
Anemia	41(49.4%)	11(26.2%)	0.013	17(20.5%)	2(4.8%)	0.021
Leukopenia	36(43.4%)	7(16.7%)	0.003	6(7.2%)	2(4.8%)	0.595
Thrombocytopenia	21(25.3%)	3(7.1%)	0.015	3(3.6%)	0	0.550
Liver function abnormalities	35(42.2%)	20(47.6%)	0.562	4(4.8%)	1(2.4%)	0.663
Renal function abnormalities	16(19.3%)	2(4.8%)	0.029	4(4.8%)	0	0.299

in situ, multifocality, tumor size, clinical stage, pathological grade, lymph node metastasis, and recurrence [17]. This study found that the HER2 positivity rate in MIBC patients was 57.6%, and HER2 positivity was significantly associated with tumors larger than 3 cm, multifocal tumors, T3 stage tumors, high-grade tumors, and pelvic lymph node metastasis. The current study also found that 79.3% of patients with pelvic lymph node metastasis were HER2 positive, which may suggest that HER2 expression is related to bladder cancer aggressiveness.

Examining cTURBT combined with GC chemotherapy, Helal et al. reported that among MIBC patients administered TURBT combined with chemoradiotherapy, HER2-negative patients had significantly better DFS and OS than HER2-positive counterparts and described HER2 as a potential therapeutic target for MIBC [18]. In this study, tumor recurrence rate in the GC treatment group of HER2-positive patients was 67.5%, with a median RFS of 19.0 months and a median OS of 56.0 months. Tumor recurrence rate in HER2-negative patients was 56.5%, with a median RFS of 36.0 months and non-reached median OS. HER2-negative patients had significantly better prognosis than HER2-positive cases. These results suggest that HER2 positivity is associated with the prognosis of patients with bladder cancer.

In HER2-positive MIBC patients, a study reported an objective response rate (ORR) for RC48-ADC treatment in locally advanced or metastatic MIBC after previous systemic chemotherapy of 50.5%, and PFS and OS of 5.9 months and 14.2 months, respectively [19]. This study showed that in the RC48-ADC group, 15 out of 42 patients (35.7%) experienced recurrence during the follow-up period and 2 (4.8%) died, with median RFS and median OS not reached; in the GC group, 56 out of 83 patients (67.5%) experienced recurrence and 22 (52.4%) died, with a median RFS of 19.0 months and a median OS of 56.0 months. The RC48 group had better RFS and OS benefits than the GC group. Retrospective analyses have shown that HER2 expression is associated with poor prognosis in urothelial carcinoma [20], and antitumor drug treatment targeting HER2 is expected to improve the prognosis of urothelial carcinoma patients.

In HER2-negative or HER2 low-expressing patients, RC48-ADC treatment was not administered in this work. This was a retrospective analysis based on the principles of clinical treatment guidelines and drug indications. Studies have reported that HER2 low-expressing patients can also benefit from anti-HER2 ADC treatment, e.g., the RC48-C011 study applying RC48-ADC in HER2 low-expressing urothelial carcinoma patients reported an ORR of 26.3%, with median PFS and OS of 5.5 months and 16.4 months, respectively, which may be related to the heterogeneity of HER2 expression and the tumor bystander effect [21].

In terms of adverse reactions, the RC48-ADC treatment group had lower incidence rates of any-grade and grade ≥ 3 adverse reactions compared with the GC treatment group. The RC48-ADC treatment group had

higher rates of liver function abnormalities, alopecia, fatigue and anemia which generally returned to normal after discontinuing the medication for 2 weeks or after receiving liver protection. Alopecia could also significantly ease after treatment end.

This study also had limitations. Firstly, this was a retrospective analysis, with inherent biases. Secondly, immunohistochemical staining is a commonly used method for clinical detection of HER2 expression levels in patients, and it is also recommended as a HER2 expression detection method in the Guidelines of Chinese Society of Clinical Oncology (CSCO): Urothelial Cancer. Immunohistochemistry combined with in situ hybridization (FISH) validation is the most accurate HER2 expression detection method. However, due to insufficient funding and technology, we did not validate the HER2 expression using FISH testing. In addition, it was a single-center study, and future prospective, multi-center, randomized controlled studies are needed to confirm the therapeutic value of RC48-ADC for MIBC.

In conclusion, the present study confirms that cTURBT combined with RC48-ADC treatment for HER2-positive MIBC is superior to combined GC treatment in terms of RFS and OS, representing an effective treatment regimen for bladder preservation in MIBC patients.

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Authors' contributions
All authors contributed to the study. Yatong Chen and Fei Luo acquired the data. Tingji Zhang carried out the analysis. Yatong Chen wrote the manuscript. Fei Luo and Jian Li participated in study design and coordination. All authors contributed to the interpretation of results and manuscript drafting. All authors approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the ethics committee of Tianjin Union Medical Center. All patients and their family members provided signed informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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