Retrospective evaluation of the effects of intra-arterial chemotherapy combined with intravesical BCG immunotherapy versus BCG immunotherapy in high-risk non-muscle-invasive bladder cancer after transurethral resection of the bladder tumor

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Research Article

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Abstract

Purpose

To develop a novel combination therapy for high-risk non-muscle-invasive bladder cancer (NMIBC) after transurethral resection of bladder tumor (TURBT), namely, intra-arterial chemotherapy (IAC) plus BCG immunotherapy, and to compare the feasibility and safety of the two therapies.

Materials and methods

A retrospective review was conducted on the data of 134 patients who were diagnosed with high-risk NMIBC and underwent TURBT in the past five years. A total of 134 patients were initially enrolled and screened according to inclusion criteria, and the remaining 103 patients were divided into two groups according to the aspiration of patients: both groups received intravesical BCG immunotherapy, and the BCG + IAC group received 4 courses of extra intra-arterial chemotherapy. Clinical and follow-up data were recorded and processed using a statistical software.

Result

The recurrence rate was 14% in the BCG + IAC group and 28.3% in the BCG group, whereas the progression rates were 7% and 8.3%, respectively. In the Kaplan-Meier plot, a statistically significant difference was observed with respect to recurrence-free survival ($p = 0.045$), while the progression-free survival of the two groups was similar ($p = 0.452$). 46.5 the patients with adverse effects of IAC and 84.5% patients suffered from adverse reactions to BCG immunotherapy, and most of the adverse effects were mild and tolerable. Univariate analysis indicated that only history of recurrence was an independent risk factor for recurrence.

Conclusion

Intra-arterial chemotherapy could decrease the recurrence rate of BCG immunotherapy in high-risk patients with NMIBC with little additional toxicity. This could be a promising auxiliary treatment for BCG immunotherapy.

Introduction

Bladder cancer is the 9th most commonly diagnosed cancer worldwide, with an estimated 470000 new cases and 200000 deaths in 2020(Taylor et al. 2020, Lenis et al. 2020, Siegel et al. 2022). It is reported that 1 in 100 men and 1 in 400 women will be diagnosed with bladder cancer sometime in life, and currently, more than 1.65 million people worldwide suffer from bladder cancer (Richters et al. 2020). Non-muscle invasive bladder cancer (NMIBC), which includes diseases confined to the mucosa (carcinoma in

situ (CIS), Ta) and submucosa (T1), accounts for approximately 75% of these cases(Tse et al. 2019, Burger et al. 2013). The European Organization for Research and Treatment of Cancer (EORTC) risk tables are widely used for NMIBC risk classification to estimate the probabilities of recurrence and progression. According to these tables, the European Association of Urology (EAU) guidelines recommend categorizing patients into low-risk, intermediate-risk, and high-risk tumors groups(Babjuk et al. 2022). Transurethral resection of bladder tumor (TURBT) following intravesical instillation is the standard treatment for high-risk NMIBC(Babjuk et al. 2022). It is well established that intravesical BCG immunotherapy is superior to chemotherapy in reducing recurrence and progression, particularly in intermediate-high risk NMIBC(Taylor et al. 2020). According to a review, BCG immunotherapy induces initial complete response rates of 55–65% for high-risk papillary tumors and 70–75% for CIS. However, there are still 25–45% of patients will not benefit from BCG therapy, and up to 40% of patients will eventually relapse(Pettenati and Ingersoll et al. 2018). Intra-arterial chemotherapy (IAC) has been proven to be an effective way to control micro-metastasis by elevating local drug concentrations(Eapen et al. 2004, Han et al. 2014, Miyanaga et al. 2000, Miyata et al. 2015), and has already been used in treating bladder cancer since the 1970s(Kubota et al. 1989). Our previous studies have already revealed that IAC combined with intravesical chemotherapy (IVC) could reduce the recurrence and progression rate of high-risk NMIBC compared to IVC alone(Chen et al. 2013, Huang et al. 2019, Huang et al. 2019). Furthermore, IAC + IVC was as effective as BCG with similar recurrence rate(Huang et al. 2021). This suggests that IAC could be an additional treatment that may decrease the recurrence rate of BCG immunotherapy. The purpose of this study was to evaluate the efficacy and safety of IAC + BCG combination therapy for high-risk NMIBC. The outcomes could open up new possibilities for the treatment of NMIBC.

Materials And Method

Patients

In this study, we retrospectively enrolled patients who were pathologically diagnosed with high-risk NMIBC after TURBT for nearly 5 years at our hospital. According to EAU stratification(Babjuk et al. 2022), high-risk NMIBC consists of any of the following standards: 1) T1 tumor; 2) G3 (HG) tumor; 3) carcinoma in situ (CIS); and 4) multiple, recurrent, and large (> 3 cm) TaG1G2/LG tumors (all features must be present). All participants were recommended to receive BCG instillation combined with IAC. Patients who feared for extra adverse events or the cost of IAC received BCG immunotherapy alone. In total, 134 patients were included and underwent a second TURBT within 4 weeks of the initial resection. Patients in the BCG + IAC group underwent combination therapy, while others received intravesical BCG immunotherapy alone. For various reasons, 31 patients were excluded, and the findings of the study were mainly based on the remaining 103 patients. All subjects conformed to the treatment schedule, and those who had previously received intravesical chemotherapy or picibanil treatment or withdrew from the treatment halfway were excluded. This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Intravesical bacillus Calmette- Guérin (BCG) immunotherapy treatment protocol

All patients received intravesical BCG immunotherapy after TURBT. The instillation schedule rests with the manufacturer's recommendations, in which induction courses included 6 cycles of weekly instillation, while the maintenance schedule included intensive instillation at three intervals: 3, 6, and 12 months in the first year, and every 6 months thereafter for 2 additional years. Reconstituted BCG (120 mg diluted in 50 ml of 0.9% saline) was maintained inside the bladder for 2 h.

BCG combined with Intra-arterial chemotherapy (IAC) treatment protocol

Patients in the IAC + BCG group received 4 courses of extra intra-arterial chemotherapy with an interval of 1 month when the first IAC was implemented within 1 month after TURBT. Each time an IAC treatment was performed, an angiographic catheter was selectively placed into the patients' internal iliac arteries using Seldinger's percutaneous technique, and cisplatin (60 mg/m2) and epirubicin (50 mg/m2) were then administered to local blood vessels through the catheter. Routine blood examinations and blood biomedical detection were performed before and after every IAC treatment. To avoid adverse gastrointestinal reactions, all participants were subsequently prescribed proton pump inhibitors.

Follow-up and outcomes

After surgery, all patients were recommended to undergo cystoscopy every 3 months for a 2-year period and then every 6 months for a 3-year period. When a suspicious mass was discovered, bladder biopsy was performed to identify the nature of the mass and its stage and grade. Specialists conducted follow-up through telephone inquiries and inspection of the information system of our hospital and recorded the outcomes. Recurrence was defined as intravesical tumor recurrence or metastasis. Progression was defined as tumor progression to T1-4stage or metastasis. Adverse effects of IAC and BCG instillation were scored and recorded according to the Common Terminology Criteria for Adverse Effects (CTCAE v4.0) grading system.

Statistical analysis

All data were organized, analyzed, and tabulated using the statistical package for social science (SPSS) software, version 25.0. All tests were two-sided, and p value below 0.05 was considered statistically significant. Overall survival, recurrence rate, progression rate, and time to first recurrence were calculated. Recurrence and progression curves were processed with Kaplan-Meier analysis. The characteristics of patients in the two groups were compared using independent sample t-tests, rank-sum tests, and Chi-square tests. The Chi-squared test was used for categorical parameters. The t-test was used for continuous parameters conforming to the normal distribution law, while the rank-sum test for non-normal distribution parameters.

Results

A total of 134 patients were initially enrolled in the study, and 31 patients were finally excluded (Fig. 1). The records of the remaining patients, including 43 patients in the BCG + IAC group and 60 patients in the BCG alone group, were analyzed. The patients' characteristics are summarized in Table 1, in which no statistically significant difference was found between the two groups. The recurrence intervals of the two groups ranged from 12 to 35 and 3 to 29 months, respectively, and the median recurrence intervals of the two groups were 18 and 11 months, respectively ($p = 0.388$). The progression intervals of the BCG + IAC and BCG alone groups ranged from 9 to 33 months and 9 to 22 months, with median progression intervals of 18 and 15 months, respectively ($p = 0.288$). The follow-up times of the two groups ranged from 10 to 57 and 11 to 56 months, and the median follow-up times were 22 and 23.5 months, respectively. The recurrence rates of the two groups were 14% (6/43) and 28.3% (17/60), respectively, and there was no statistically significant difference between the BCG + IAC and BCG alone groups according to the Chi-square test ($p = 0.084$). The rates of progression were 7% (3/43) and 8.3% (5/60), respectively, with no significant difference ($p = 1.000$). The overall survival of the two groups was similar ($p = 1.000$), even though the BCG + IAC group seemed to be higher (97.7% vs. 96.7%). One of the patients in BCG + IAC group died of severe pulmonary infection, while in the BCG alone group, one patient died of pulmonary metastasis of bladder cancer, and another died from renal failure. The results of these comparisons are summarized in Table 2.

Table 1
Patient and tumor characteristics

	Overall(n = 103)	BCG + IAC(n = 43)	BCG(n = 60)	*P* value
Age, years				0.43※
Mean ± SD	63.48 ± 1.16	64.95 ± 1.43	62.42 ± 1.70	
Median	65	67	64.5	
Range	33–88	36–82	33–88	
Gender, n (%)				0.908
Males	82(79.6)	34(79.1)	48(80)	
Females	21(20.4)	9(20.9)	12(20)	
Grade, n (%)				0.928
Low grade	14(13.6)	6(14.0)	8(13.3)	
High grade	89 (86.4)	37(86.0)	52(86.7)	
T category (n%)				0.434
Ta	18(17.5)	9(20.9)	9(15.0)	
T1	85(82.5)	34(79.1)	51(85.0)	
CIS (n%)				0.730
No	90(87.4)	37(86.0)	53(88.3)	
Yes	13(12.6)	6(14.0)	7(11.7)	
Tumor size (n%)[a]				0.236
3cm	65(63.1)	30(69.8)	35(58.3)	
≥3cm	38(36.9)	13(30.2)	25(41.7)	
Multifocal (n%)				0.818
No	30(29.1)	12 (27.9)	18(30)	
Yes	73(70.9)	31(72.1)	42(70)	
History of recurrence (n%)				0.108
No	71(68.9)	33(76.7)	38(63.3)	

[a]Maximum size of largest tumor resected

※Analyzed with Mann-Whitney U test

	Overall(n = 103)	BCG + IAC(n = 43)	BCG(n = 60)	*P* value
Yes	32(31.1)	10(23.3)	22(36.7)	
[a]Maximum size of largest tumor resected				
※Analyzed with Mann-Whitney U test				

Table 2
Clinical outcome of high-risk patients in BCG + IAC and BCG groups

	BCG + IAC	BCG	*P* value
Tumor recurrence rate	14% (6/43)	28.3% (17/60)	0.084
Median recurrence interval	18 (months)	11 (months)	0.388
Tumor progression rate	7% (3/43)	8.3% (5/60)	1.000
Median progression interval	18 (months)	15 (months)	0.288
Median follow-up time	22 (months)	23.5 (months)	0.303
Overall survival	97.7% (42/43)	96.7% (58/60)	1.000

The Kaplan-Meier curves for recurrence-free survival (RFS) and progression-free survival (PFS) are shown in Figs. 2 and 3. The BCG + IAC group had a higher estimated RFS rate (86.0% vs. 71.7%, p = 0.049, Fig. 2), while the PFS of the two groups seemed to be similar (93.0% vs. 91.7%, p = 0.452).

Univariate analysis was performed for tumor-related factors, and the p-value was set at 0.05. History of recurrence was found to be the only independent risk factor for recurrence (HR 3.971; CI: 1.717–9.184). The results are presented in Tables 3 and 4.

Table 3
Univariate analysis according to recurrence

Factor	HR (95% CI)	*P* value
Sex		
Female vs male	0.433 (0.175–1.074)	0.088
Age (years)		
65 vs ≥ 65	0.970 (0.423–2.222)	0.942
History of recurrence		
No vs yes	3.971 (1.717–9.184)	0.001※
Tumor size (cm)		
3 vs ≥ 3	1.008 (0.435–2.337)	0.985
T category		
Ta vs T1	0.570 (0.224–1.450)	0.261
Grade		
Low vs high	0.473(0.186–1.202)	0.140
CIS		
No vs yes	2.163(0.848–5.516)	0.131
CI confidence interval, *HR* hazard ratio		
※Significant difference		

Table 4
Univariate analysis according to progression

Factor	HR (95% CI)	*P* value
Sex		
Female vs male	0.244(0.055–1.076)	0.084
Age (years)		
65 vs ≥ 65	1.016(0.950–1.086)	0.644
History of recurrence		
No vs yes	2.715(0.677–10.877)	0.167
Tumor size (cm)		
3 vs ≥ 3	0.210(0.026–1.719)	0.083
T category		
Ta vs T1	0.636(0.128–3.165)	0.595
Grade		
Low vs high	0.317(0.075–1.344)	0.145
CIS		
No vs yes	3.466(0.818–14.673)	0.117
CI confidence interval, *HR* hazard ratio		

Adverse reactions were reviewed according to CTCAE v4.0 and summarized in Table 5 and Table 6 respectively. In the BCG + IAC group, 46.5% (20/43) of patients experienced adverse complications of intra-arterial chemotherapy, of which five experienced nausea and vomiting, four experienced fever, six experienced hypo-leukemia, five experienced low neutrophil count, one experienced hepatic dysfunction, and three experienced renal dysfunction. All these complications were mild, and no patient withdrew before completing the 4-course intra-arterial chemotherapy. The majority of patients in both groups experienced adverse reactions to BCG immunotherapy, of which 87 experienced cystitis, 26 experienced hematuria, and 2 experienced incontinence. Regarding systemic complications, 38 patients had fever and 21 patients experienced flu-like symptoms. Owing to severe adverse reactions, eight patients in the BCG + IAC group and four in the BCG alone group discontinued the treatment. The adverse reactions to BCG in the two groups were compared, and no significant difference was found between the BCG + IAC and BCG alone groups.

Table 5
Adverse reaction of intra-arterial chemotherapy

	Grade I-II	Grade III-IV	Incidence %
Nausea/vomiting	5	-	11.6
Fever	4	-	9.3
Hypo-leukemia	6	-	14.0
Neutropenia	5	-	11.6
Increase alanine aminotransferase	1	-	2.3
Increase creatinine	3	-	7.0
According to CTCAE v4.0, Common Terminology Criteria for Adverse Events, version 4			

Table 6
Adverse reaction of BCG immunotherapy

	Grade I-II	Grade III-IV	Incidence %
Local			
Cystitis	75	12	84.5
Hematuria	26	-	25.2
Incontinence	-	2	1.9
Systemic			
Fever	38	-	36.9
Flu-like symptoms [a]	21	-	20.4
According to CTCAE v4.0, Common Terminology Criteria for Adverse Events, version 4.0			
[a]Malaise/fatigue/myalgia			

Table 7
Comparison of adverse reactions of BCG immunotherapy of BCG + IAC and BCG groups

Adverse effect	BCG + IAC	BCG	*P* value
Cystitis			
Yes	38(88.4)	49(81.7)	0.418
No	5(11.6)	11(18.3)	
Hematuria			
Yes	9(20.9)	17(28.3)	0.394
No	34(79.1)	43(71.7)	
Incontinence			
Yes	1(2.3)	1(1.7)	1.000
No	42(97.7)	59(98.3)	
Fever			
Yes	15(34.9)	23(38.3)	0.720
No	28(65.1)	37(61.7)	
Flu-like symptoms [a]			
Yes	9(20.9)	12(20.0)	0.908
No	34(79.1)	48(80.0)	
According to CTCAE v4.0, Common Terminology Criteria for Adverse Events, version 4.0			
[a]Malaise/fatigue/myalgia			

Discussion

According to the EAU guidelines for NMIBC, BCG instillation is the standard treatment strategy for high-risk NMIBC(Babjuk et al. 2022). As many as 25–45% of patients do not benefit from intravesical BCG therapy(Pettenati and Ingersoll et al. 2018). Two earlier studies revealed that within a median follow-up time of approximately 2 years, the recurrence and progression rates were relatively high in NMIBC, even though BCG instillation was utilized(Sylvester et al. 2002, Bohle et al. 2003). Radical cystectomy (RC) is another recommended strategy for high-risk NMIBC, which carries a high risk of perioperative morbidity and mortality, especially in an old and infirm population(Tse et al. 2019). It has been suggested that RC can impair patients' gut function and metabolism, leading to malnutrition, sarcopenia and frailty(Michel et al. 2020). All these factors impact the outcomes of patients with bladder cancer. Moreover, owing to urinary diversion, radical cystectomy greatly affects the quality of life of patients. As a result, many

patients prefer to reject surgery because of the concern of decline in living standards. To decrease the recurrence rate and delay the progression of NMIBC, so that eventual RC surgery could be avoided, various alternative treatment options for high-risk NMIBC patients have emerged in recent years, including hyperthermia chemotherapy and BCG + checkpoint inhibitor therapy(Pettenati and Ingersoll et al. 2018, Veeratterapillay et al. 2016). However, there is currently a lack of rigorous evidence on the effectiveness of these strategies.

Among BCG combination therapies, intra-arterial chemotherapy (IAC) is rarely mentioned, which was first used in muscle-invasive bladder cancer and has proven to preserve the bladder or prolong life(Eapen et al. 2004, Han et al. 2014, Miyanaga et al. 2000, Miyata et al. 2015). Our previous studies reported that IAC + IVC was superior to IVC alone in preventing tumor recurrence and progression in NMIBC(Chen et al. 2013, Huang et al. 2019, Huang et al. 2019). Another study revealed that, compared to BCG immunotherapy, IVC + IAC has almost equal effects in treating NMIBC(Huang et al. 2021). The mechanism of action of BCG is currently considered to be the inflammatory response induced by BCG (Moschini et al. 2019). Cisplatin and anthracyclines are commonly used in IAC, the former kills tumor cells via oxidative stress-mediated cytotoxicity, cell apoptosis (Dasari and Tchounwou et al. 2014), while the latter achieve anti-tumor activity by preventing DNA replication in cancer cells. Certainly, these agents could supplement the anti-tumor effect of BCG owing to distinct mechanisms. Therefore, it is worth exploring whether IAC could bring a gain effect on the therapeutic effect of BCG immunotherapy and ascertaining potentially additional side effects.

In this study, we compared the parameters representing efficacy and toxicity of the two different treatment protocols. The recurrence rate in the BCG alone group was close to our previous study (28.3% vs. 26.4%)(Huang et al. 2021). However, it was slightly lower than the rate of 35.2% reported by Tom J.H et al.(Arends et al. 2016) We attribute this to the fact that BCG-treated patients in Tom J.H et al.'s study started the treatment in at least 3 weeks after TURBT rather than in two weeks in our study, indicating that earlier instillation of BCG might be a key influence of recurrence. In contrast, within the median follow-up time of 22 months, the recurrence rate in the BCG + IAC group was 14.0%. The Kaplan-Meier survival analysis showed that the difference in recurrence rate between the two groups was remarkable ($p < 0.05$), suggesting that IAC could further reduce the recurrence rate of BCG immunotherapy. It could be an effective reinforcement for the weakness of BCG immunotherapy. To explain the mechanism of IAC, Hoshi et al.(Hoshi et al. 1997) performed a series of animal surgeries on rabbits and found that due to direct arterial administration, antitumor drug concentrations in the plasma and bladder tumors were much higher in the IAC group. Higher drug concentrations could lead to the reduction of potential micrometastases into smooth muscle or pelvic lymph nodes and, therefore, decrease the incidence of recurrence.

Compared to two earlier studies, the progression rate of the IAC + BCG group in our study was quite lower (7.0% vs. 25.3% and 36%)(Palou et al. 2018, Thiel et al. 2019). Unfortunately, there was no significant difference in the progression rate between the two experimental groups ($p = 0.288$). However, it is widely accepted that long-term accumulation of genetic alterations in cancer cells plays a crucial role in tumor

progression(Yokota et al. 2000). Eradicating more residual mutated cells after TURBT at an early stage will most likely delay NMIBC progression. Moreover, according to a systematic review(van den Bosch and Alfred Witjes et al. 2011), progression in high-risk NMIBC mainly occurs within 48 months, and the median follow-up times of our study haven't reach the time limit yet. Hence, we firmly believe that IAC + BCG therapy has better clinical efficacy in delaying NMIBC progression. Continuation of follow-up and further prospective studies are required to verify our hypotheses.

Regarding the safety, routine blood changes and gastrointestinal distress were the most common complications. Approximately 46.5% of patients (20/43) experienced adverse effects of IAC. According to the CTCAE v4.0 grading system, the grades of adverse reactions were limited to grade 1 to 2, meaning that they were mild enough to be managed at home or outpatient. These results consist with previous studies.(Huang et al. 2019, Huang et al. 2021, Lian et al. 2019) On the contrary, including patients who previously withdrew, 86.1% patients (99/115) suffered from adverse reactions of BCG immunotherapy. Notably, eight patients in the BCG + IAC group discontinued treatment because of serious side effects of BCG rather than IAC. No statistically significant difference in side effects was observed between the two groups, indicating that IAC causes reversible and tolerable adverse reactions and brings no additional toxicity to BCG instillation.

Our study has a few limitations. The study had a retrospective design, leading to inevitable bias within the data collection procedure. The follow-up time was not long enough, probably limiting the strength of the conclusion. Inadequate follow-up time also caused a negative result in the comparison of progression rates. The median follow-up times of the two previous studies are much longer than that of our study (5.2 years and 100 months, respectively). With follow-up work continue, combination therapy will definitely show better efficacy in preventing tumor progression. What's more, it is widely known that tumor grade, stage, CIS, history of recurrence, etc. are all risk factors for recurrence and progression. However, in our current study no other risk factors were found to be related to recurrence, and no parameters were significantly associated with progression. We attribute this limitation to the small sample size and the finite time span. To solve these problems, further multicenter, large-scale prospective studies are recommended.

Conclusion

The present study indicated that IAC + BCG combination therapy in terms of preventing recurrence, was superior to BCG alone in high-risk NMIBC. IAC is likely compatible with BCG instillation, with acceptable adverse reactions. Hence, it could be a promising auxiliary treatment for standard BCG immunotherapy in high-risk NMIBC to further reduce the recurrence even progression rates.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by Shuhang Luo, Rui Yang, Wusimanjiang, Jiahao Lei and Jinwen Liu. Data analysis was performed by Shuhang Luo, Shengjie Lin and Zhoujing Liu. The first draft of the manuscript was written by Shuhang Luo and Rui Yang. Critical revision and supervision were performed by Bin Huang, Junxing Chen and Lingwu Chen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of their data.

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Figures

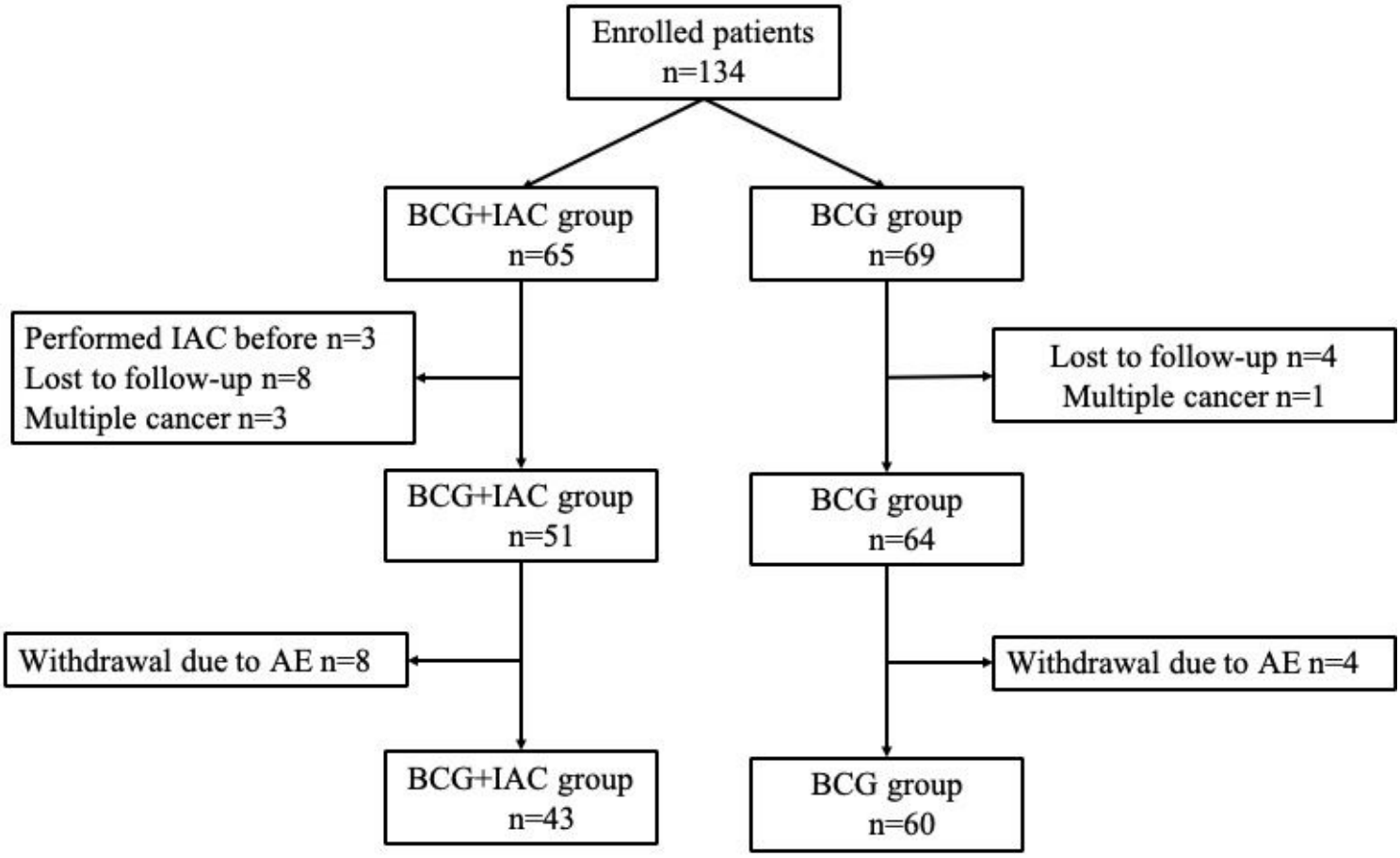

Figure 1

Flow diagram of this study: IAC: Intra-arterial chemotherapy. BCG: intravesical bacillus Calmette–Guérin immunotherapy. AE: Adverse Events

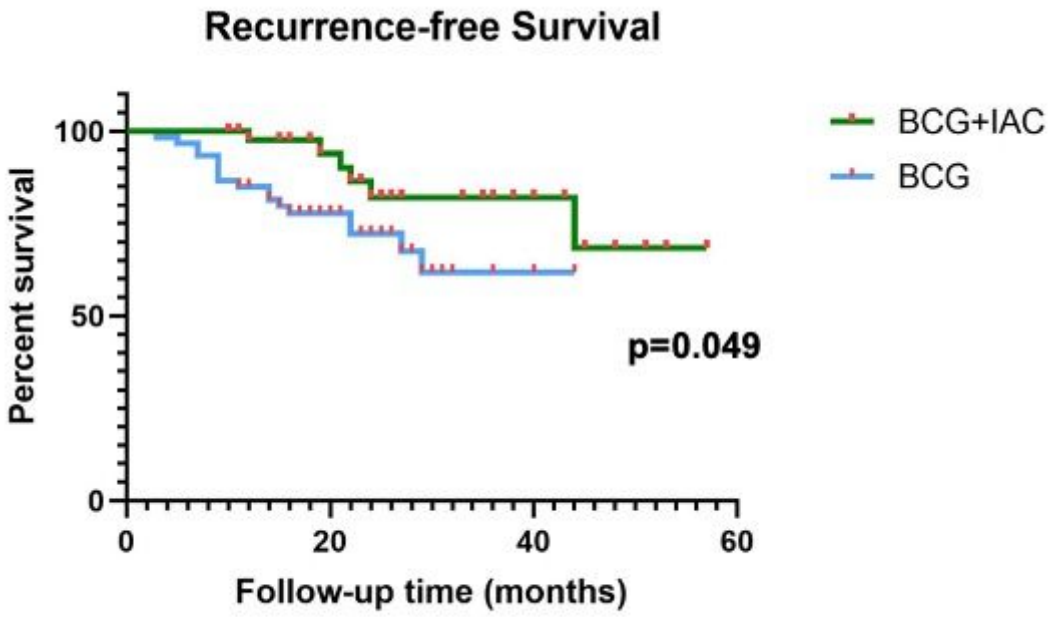

Figure 2

Kaplan–Meier curves for recurrence-free survival are shown. A statistically significant difference was found between the two groups.

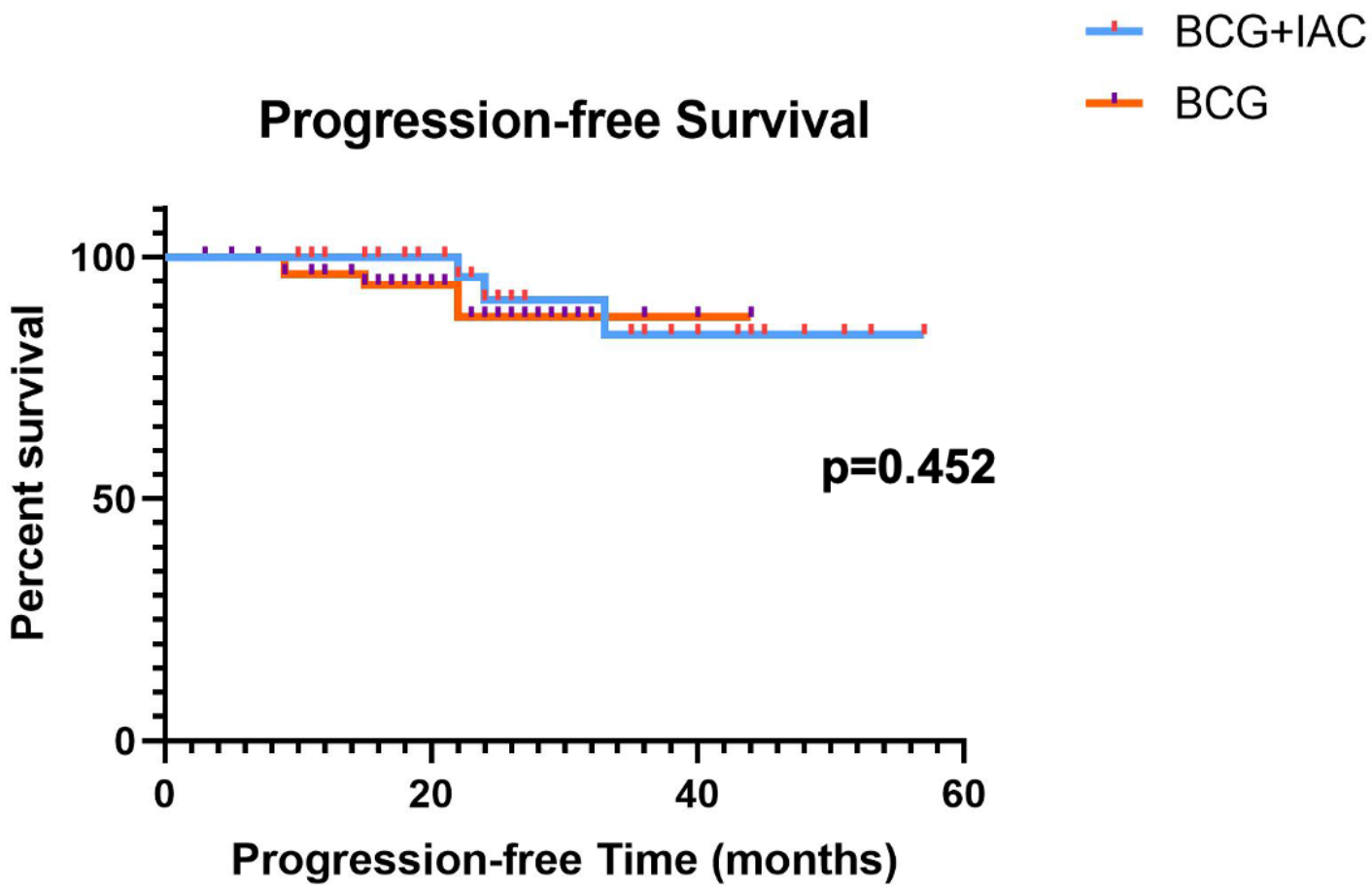

Figure 3

Kaplan–Meier curves for progression-free survival are shown. There was not statistically significant difference in Kaplan–Meier curves for progression-free survival between the two groups