Journal of Cancer Research and Clinical Oncology (2019) 145:1625–1633
https://doi.org/10.1007/s00432-019-02900-8

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Intra-arterial chemotherapy combined with intravesical chemotherapy is effective in preventing recurrence in non-muscle invasive bladder cancer

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Received: 28 December 2018 / Accepted: 18 March 2019 / Published online: 21 March 2019

Abstract

Objective To evaluate the efficacy and safety of intra-arterial chemotherapy (IAC) combined with intravesical chemotherapy (IC) in non-muscle invasive bladder cancer (NMIBC) and identify the risk factors for recurrence and progression.

Methods This is a retrospective cohort study of NMIBC patients in south China. Ninety-nine patients underwent IAC combined with transurethral resection of bladder tumor (TURBT) and IC, and 50 patients underwent TURBT plus IC without IAC. The 5-year outcomes of the two groups were compared. Cox regression was used to evaluate risk factors. Kaplan–Meier curves were used to assess the significant differences of recurrence-free survival and progression-free survival.

Results At 5 years, IAC significantly reduced the recurrence of high-grade NMIBC, 54.5% (18/33) in the non-IAC group vs 30.5% (18/59) in the IAC group ($p=0.028$). IAC significantly reduced the recurrence of high-risk NMIBC, 56.3% (18/32) in the non-IAC group vs 26.1% (18/69) in the IAC group ($p=0.007$). IAC significantly reduced the recurrence of intermediate-risk NMIBC, 44.4% (8/18) in the non-IAC group vs 22.2% (6/27) in the IAC group ($p=0.030$). Tumors numbering from 2 to 7 had the highest recurrence rate (18.1%, 27/149). In this aspect, there was a significantly lower recurrence rate in the IAC group (30.8%, 12/30) than in the non-IAC group (68.2%, 15/22) ($p=0.007$). No significant difference was found in the progression rate between the two groups. Only two cases (2/99, 2.0%) in the IAC group showed progression. The results of univariate and multivariate analyses suggested that the number of tumors, grade and risk level were risk factors for recurrence. No difference was found with respect to gender, age, tumor diameter, and T category. In the Kaplan–Meier plot, recurrence-free survival was significantly associated with treatment strategies ($p<0.01$). Recurrence-free survival was shorter in the non-IAC group (12.73 ± 7.56 months) than in the IAC group (17.88 ± 12.26 months).

Conclusions Combined IAC is a promising procedure to prevent recurrence and may be useful to suppress progression in NMIBC patients. The independent risk factors for the recurrence of NMIBC were multifocal tumors, grade and risk level. Intra-arterial chemotherapy is an effective and safe procedure and may be a promising choice in areas where BCG is not available or for patients who are intolerant to BCG.

Keywords Non-muscle invasive bladder cancer · Intra-arterial chemotherapy · Recurrence · Progression

Background

Urothelial bladder cancer (UBC) is one of the most prevalent malignancies in China. UBC is a heterogeneous disease regarding its clinical and biological features (Miyake et al. 2016). Up to 75–85% of UBC do not invade the muscle (non-muscle-invasive bladder cancer, NMIBC) (Burger et al. 2013). NMIBC is characterized by a high recurrence rate (30–85%), despite advancements in surgical techniques and adjuvant intravesical treatment, which makes NMIBC one of the most costly cancers for lifetime treatment (Knowles and Hurst 2015; Witjes et al. 2014; Reis et al. 2016). Therefore, there is a need to improve the treatment strategies for NMIBC. Transurethral resection of bladder tumor (TURBT) followed by intravesical administration of Bacille Calmette–Guérin (BCG) or chemotherapy is a standard treatment recommended by the guidelines of the American Urological Association and European Association of Urology

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for carcinoma in situ (CIS), T1 and high-risk Ta tumors (Donald et al. 1991; Hall et al. 2007; Babjuk et al. 2017). Despite this therapy, nearly 40% patients suffer recurrence within 2 years (Nepple et al. 2010).

A small number of previous studies have suggested that bilateral iliac artery perfusion of chemotherapy may reduce the recurrence and progression of bladder cancer (Chen et al. 2009; Eapen et al. 2004; Cambier et al. 2016). Intra-arterial infusion of chemotherapy is well tolerated and reported to be effective in localized bladder cancer. However, its effectiveness in comparison to other forms of therapy in NMIBC is still unclear.

The aim of the present study was to explore the effectiveness of intra-arterial chemotherapy in combination TURBT + adjuvant intravesical treatment in patients with NMIBC and to discern risk factors of a poor outcome. Our findings suggest that combined IAC is a promising treatment.

Methods

We retrospectively analyzed all NMIBC patients admitted to the first affiliated hospital of Sun Yat-sen University from June 2005 to June 2015. The clinical and pathologic features of the patients were reviewed, including demographic characteristics, pathologic grade and stage, tumor size, number, shape, location, presence of CIS, recurrence status, progression status, treatments, and adverse events.

Criteria for inclusion were as follows: (1) NMIBC patients undergoing TURBT + adjuvant intravesical treatment; (2) histopathological diagnosis of transitional-cell carcinoma, the presence of primary NMIBC; (3) patients with a follow-up time of at least 5 years or until death, full data available.

Criteria for exclusion were as follows: (1) MIBC or distant metastasis beyond the pelvis; (2) histopathological diagnosis of non-transitional-cell carcinoma; (3) bladder cancer patients taking an oral anticoagulant with an increased risk of bleeding; (4) ineligible for intra-arterial chemotherapy; (5) serum urea/creatinine > twice normal; (6) uncontrollable urinary tract infections; and (7) leukopenia/thrombopenia.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Ethics Committee of the first affiliated hospital of Sun Yat-sen University.

Data on bladder cancer recurrence, progression, therapeutic protocols and treatment outcomes were recorded.

The primary recurrence endpoint was defined as the reoccurrence of tumor at any grade and any stage during follow-up. Any-grade recurrence included recurrence with low-grade and high-grade recurrence.

Early recurrence was defined as reoccurrence of the tumor within 4.5 month after TURBT (Cambier et al. 2016). Recurrence-free survival was defined as the date of TURBT to the date of first documented clinical recurrence. Progression was defined as the confirmation of muscle-invasive lesions (T2), invasion beyond the bladder tissue (T3/T4), or metastatic disease by tissue biopsy. Progression-free survival was defined as the date of TURBT to the date of first documented clinical progression and metastasis. Other evaluated end points included overall survival (OS), cancer-specific survival (CSS), and muscle-invasive-free survival (MIFS). Overall survival was defined as the date from diagnosis until the date of death resulting from any cause. Cancer-specific survival was defined as the date from diagnosis until the date of death resulting from bladder cancer. Muscle-invasive-free survival was defined as the date from TURBT to the date of the first documented muscle invasive lesion (Brown et al. 2007; Chappidi et al. 2016; Kamat et al. 2016).

Classification of risk level was based on the EORTC-GUCG risk scoring system: (1) low risk: primary, solitary, Ta, low-grade/G1, < 3 cm and no CIS; (2) intermediate risk: all tumors not defined in the 2 adjacent categories (between the category of low and high risk); and (3) high risk: (a) T1 tumor, (b) high grade/G3 tumor, (c) CIS, and (d) multiple, recurrent and large (> 3 cm) Ta G1G2 tumors (all conditions must be present at this point) (Sylvester et al. 2006). G1 and G2 were defined as low-grade tumors, and G3 was defined as high-grade tumor (Sun et al. 2017).

Treatment protocol

TURBT was performed based on a standardized procedure based on the international recommendation in our hospital (Miyake et al. 2015).

Adjuvant intravesical treatment

Intravesical instillation chemotherapy with epirubicin (50 mg/50 mL) was performed immediately after TURBT in both groups. Epirubicin was maintained in the bladder for 1 h. Intravesical instillation chemotherapy was administered for 4–8 consecutive weeks and then monthly for 6–12 consecutive months (Babjuk et al. 2017; Bosschieter et al. 2017; Marttila et al. 2016; Arends et al. 2016).

Intra-arterial chemotherapy

The percutaneous catheter system (PCs) was placed in the bilateral internal iliac arteries distal to the superior gluteal arteries using a modified Seldinger technique.

Patients were administered intra-arterial chemotherapy through PCs with epirubicin (50 mg/m^2) and cisplatin

(60 mg/m^2) 2 weeks after TURBT. The treatment was repeated every 4–6 weeks. Patients received 3 cycles of treatment unless they presented disease progression or suffered intolerable side effects (Chen et al. 2009, 2013; Sun et al. 2017).

Follow-up

Cystoscopy was performed every 3 months during the first 2 years and every 6 months thereafter. The CT urogram was performed at 3 months postoperatively and then every 6–12 months thereafter.

Ethics, consent and permissions

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the first affiliated hospital of Sun Yat-sen University (permission number: 475109). All participates were informed and consented to the research before they were enrolled in the study.

Consent to publish

The authors have obtained consent to publish from the participants.

Statistical analysis

Descriptive statistics were used for patient characteristics. The Mann–Whitney *U* test and *t* test were used to compare continuous variables among two groups, and the Chi square test was used to compare categorical variables. The mean ± standard deviation (SD) is presented for continuous and ordinal data, while categorical data are presented as the absolute count and percentage. A p value < 0.05 was considered significant.

Univariable and multivariable Cox proportional hazards models were used to evaluate risk factors (age, sex, T category, number of tumors, diameter of tumors, grade, risk level, etc.) for recurrence and progression. Items that were statistically significantly associated in the univariate analysis were used as input in the multivariate analysis. Kaplan–Meier curves were used to assess the significant differences of recurrence-free survival and progression-free survival for the entire study group, and the equivalences of the survival curves were tested using log-rank tests.

A p value < 0.05 was considered significant.

All statistical analyses were performed using SPSS version 23 statistical software.

Results

Baseline characteristics

A total of 149 NMIBC patients were enrolled, of which 50 underwent TURBT + intravesical treatment and 99 underwent TURBT + intravesical treatment in combination with intra-arterial chemotherapy.

Patient and tumor characteristics are listed in Table 1. Of the total cohort, 139 (93.3%) were male and 10 (6.7%) were female, and the mean (SD) age of the present study was 61.54 ± 12.71 years. No significant differences were found between the two groups regarding age, gender, T category, number of tumors, diameter of tumors, grade and risk.

The 5-year clinical outcomes

Clinical outcomes were compared between the two groups (Table 2).

Table 1 Demographic and baseline characteristics of the NMIBC patients

	IAC		*p*
	Yes (n = 99)	No (n = 50)	
Age [mean (SD)]	60.65 (12.64)	63.30 (12.79)	0.233
Male (n%)	92 (92.9%)	47 (86.0%)	0.234
Median follow-up (months, range)	24.25 (5–50)	22.30 (10–42)	0.368
Age (year)			0.172
< 60	49	18	
60–70	23	10	
> 70	27	22	
T category (n%)			0.361
Ta	63	36	
T1	36	14	
Number of tumors (n%)			0.110
1	36	23	
2–7	39	22	
> 7	24	5	
Diameter of tumors (cm)			0.281
< 3	59	35	
> 3	40	15	
Grade (n%)			0.480
Low grade	40 (40.4%)	17 (34.0%)	
High grade	59 (59.6%)	33 (66.0%)	
Risk			NA
Low risk	3	0	
Intermediate risk	27	18	
High risk	69	32	

NMIBC non-muscle invasive bladder cancer

Table 2 Clinical outcome of the NMIBC patients

	IAC		*p*
	Yes ($n=99$)	No ($n=50$)	
Recurrence (*n*%)	24 (24.2)	26 (52.0)	0.001*
Recurrence-free rate	75/99 (75.8%)	24/50 (48.0%)	0.001*
Mean recurrence time (month)	17.88	12.73	0.078
Recurrence of initiative high grade tumor			
Within 4.5 month (*n*%)	0 (0)	2 (6.1)	0.126
4.5 month–2 year (*n*%)	14 (23.7)	15 (45.5)	0.038*
2 year–5 year (*n*%)	4 (6.8)	1 (3.0)	0.651
Cumulative recurrence 5 years (*n*%)	18 (30.5)	18 (54.5)	0.028*
Recurrence of initiative low grade tumor			
Within 4.5 month (*n*%)	0 (0)	1 (5.9)	0.298
4.5 month–2 year (*n*%)	6 (15)	6 (35.3)	0.152
2 year–5 year (*n*%)	0 (0)	1 (5.9)	0.298
Cumulative recurrence 5 years (*n*%)	6 (15)	8 (47.1)	0.107
Recurrence of initiative high-risk tumor			
Within 4.5 month (*n*%)	0 (0)	2 (6.3)	0.098
4.5 month–2 year (*n*%)	14 (20.3)	15(46.9)	0.009*
2 year–5 year (*n*%)	4(1.4)	1(3.1)	1.000
Cumulative recurrence 5 years (*n*%)	18 (26.1)	18 (56.3)	0.007*
Recurrence of initiative intermediate-risk tumor			
Within 4.5 month (*n*%)	0 (0)	1 (5.6)	0.400
4.5 month–2 year (*n*%)	6 (22.2)	6 (33.3)	0.313
2 year–5 year (*n*%)	0 (0)	1 (5.6)	0.400
Cumulative recurrence 5 years (*n*%)	6 (22.2)	8 (44.4)	0.030*
Recurrence of initiative low-risk tumor			
Within 4.5 month (*n*%)	0	0	–
4.5 month–2 year (*n*%)	0	0	–
2 year–5 year (*n*%)	0	0	–
Cumulative recurrence 5 years (*n*%)	0	0	–
Number of tumors (5 year cumulative recurrence)			
> 7	3 (12.5)	2 (40.0)	0.195
2–7	12 (30.8)	15 (68.2)	0.007*
1	9 (25.0)	9 (39.1)	0.265
Diameter of tumors (5 year cumulative recurrence)			
> 3 cm	7 (11.9)	7 (20.0)	0.039*
< 3 cm	17 (28.8)	19 (54.3)	0.017*
Progression (*n*%)	2 (2.0)	4 (8.0)	0.098
Progression-free rate	97/99 (98.0)	46/50 (92.0)	0.098

NMIBC non-muscle invasive bladder cancer

Asterisk indicates the significance of the two groups with or without IAC

During the mean follow-up of 43.81 (21.43) months, 75 patients (75.8%) in the IAC group vs 24 patients (48.0%) in the non-IAC group were recurrence free ($p=0.001$).

All patients with a low-risk level before induction had no recurrence during follow-up. No cases in the IAC group had early recurrence.

Among patients initially presenting with high grade NMIBC, 54.5% (18/33) in the non-IAC group vs 30.5% (18/59) in the IAC group had recurrence after 5 years ($p=0.028$). The time range from 4.5 month to 2 years showed the highest recurrence rate, while in this time range, the IAC group had significantly fewer recurrent cases (23.7%, 14/59) than the non-IAC group (45.5%, 15/33) ($p=0.038$). Among patients initially presenting with high-risk NMIBC, 56.3% (18/32) in the non-IAC group vs 26.1% (18/69) in the IAC group had recurrence after 5 years ($p=0.007$). The time range from 4.5 months to 2 years had the highest recurrence rate, while in this time range, the

IAC group had significantly fewer recurrent cases (20.3%, 14/69) than the non-IAC group (46.9%, 15/32) ($p=0.009$). The recurrence rate of patients initially presenting with intermediate-risk NMIBC showed a similar tendency, with 44.4% (8/18) in the non-IAC group vs 22.2% (6/27) in the IAC group presenting recurrence after 5 years ($p=0.030$).

The number of tumors ranging from 2 to 7 had the highest recurrence rate (18.1%, 27/149). Thus, there was a significantly lower recurrence rate in the IAC group (30.8%, 12/30) compared with the non-IAC group (68.2%, 15/22) ($p=0.007$).

No significant differences were observed in the progression rate between the two groups. Only two cases (2/99, 2.0%) in the IAC group showed progression.

Risk factors for recurrence

Results from the univariate and multivariate analyses are shown in Table 3. Concerning recurrence, the univariate analysis revealed a significant correlation with the number of tumors, grade and risk level. In the multivariate analyses, the same significant correlations of multifocal tumors 2–7 [HR = 0.177, 95% confidence interval (CI) 0.043–0.730, $p=0.017$], high grade [HR = 3.671, 95% confidence interval (CI) 1.300–10.369, $p=0.014$] and higher risk level [HR = 4.701, 95% confidence interval (CI) 1.560–14.165, $p=0.007$] were detected. No difference was found in terms of gender, age, tumor diameter, and T category.

Kaplan–Meier analysis

Kaplan–Meier analysis demonstrated that patients on different therapeutic strategies had different outcomes.

Recurrence-free survival was significantly associated with treatment strategies ($p<0.01$). The recurrence-free survival time was shorter in the non-IAC group (12.73 ± 7.56 months) than the IAC group (17.88 ± 12.26 months). The 5-year recurrence-free survival rate was 75.8% in the IAC group vs 48.0% in the non-IAC group (Fig. 1).

However, progression was not significantly correlated with the treatment strategies ($p=0.731$) (Fig. 2).

Progression from induction initiation was not significantly different between the non-IAC group (11.15 ± 8.49 months) and the IAC group (13.71 ± 5.91 months).

Side effects

None of the patients reported intolerance related to IAC induction and maintenance therapy affecting the treatment

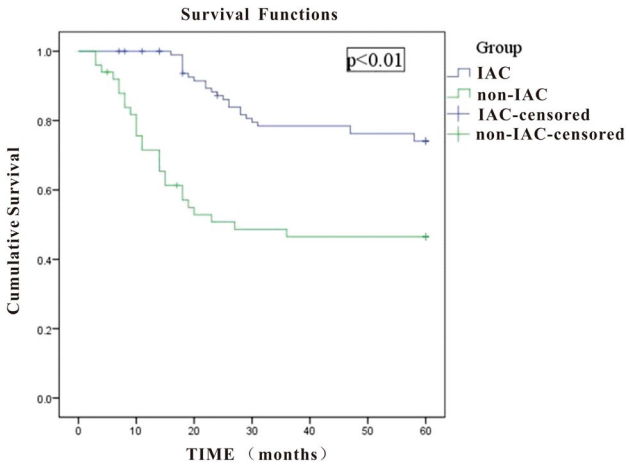

Fig. 1 Kaplan–Meier plot of recurrence-free survival for patients in the IAC and non-IAC groups

Table 3 Significant variables associated with recurrence of NMIBC on univariate and multivariate analysis

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Sex	0.981	0.274–3.513	0.977	–	–	–
Age (years)			0.529	–	–	–
< 60	Reference	–	–			
60–70	1.444	0.725–2.876	0.296			
> 70	1.470	0.671–3.223	0.336			
No. of tumor			0.003*			0.005*
1	Reference			Reference		
2–7	0.166	0.039–0.704	0.015*	0.177	0.043–0.730	0.017*
> 7	1.347	0.392–4.624	0.636	1.266	0.384–4.179	0.699
Tumor diameter	1.958	0.702–5.463	0.199	–	–	–
T category	0.993	0.322–3.061	0.991	–	–	–
Grade	3.822	1.329–10.995	0.013*	3.671	1.300–10.369	0.014*
Risk level	4.630	1.541–13.910	0.006*	4.701	1.560–14.165	0.007*

Asterisk indicates the significance of the two groups with or without IAC

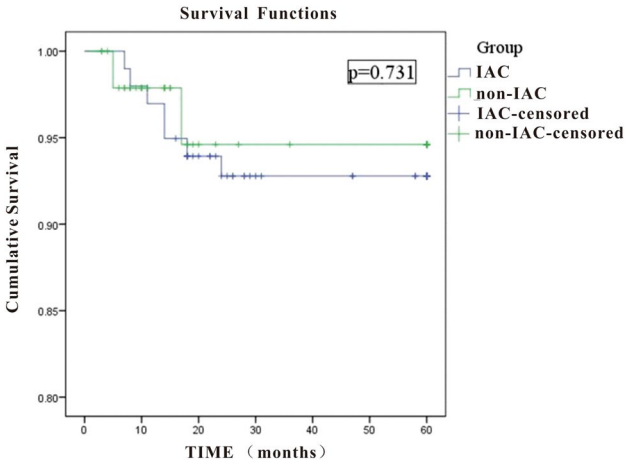

Fig. 2 Kaplan–Meier plot of progression-free survival for patients in the IAC and non-IAC groups

course. Side effects included a range of mild symptoms, such as mild anemia (2/99, 2%), thrombocytopenia (2/99, 2%), nausea and vomiting (8/99, 8.1%), and skin ulcer (1/99, 1%).

Discussion

Despite the use of standard TURBT and adjuvant intravesical treatment, the recurrence rate of the NMIBC patients in the present study reached as high as 52.0%, which was in accordance with many previous studies (Sylvester et al. 2006). Transurethral bladder tumor resection (TUR-BT) and subsequent adjuvant intravesical treatments are recommended by the American Urological Association (AUA)/Society of Urologic Oncology (SUO), European Association of Urology (EAU), and National Comprehensive Cancer Network (NCCN) (Woldu et al. 2017). Additionally, early radical cystectomy is also a recommended option for the treatment of high-risk non-muscle invasive bladder cancer (Babjuk et al. 2013). Cystectomy will lead to urinary diversion, which greatly affects quality of life and, as a result, most patients prefer to skip surgery. However, a large proportion of the patients still experience recurrence on bladder-sparing therapy, or they are BCG/chemotherapy unresponsive (Catalona et al. 1987). Chinese patients also face an additional dilemma. BCG has not been produced in large quantities for several years, so it is very difficult to acquire in most Chinese hospitals. Therefore, intravesical chemotherapy is the most readily available choice for the majority of NMIBC patients, which could be one of the reasons for the unsatisfactory outcomes. Thus, there is a need to search for alternative therapeutic methods to reduce the recurrence and progression of NMIBC.

Since the first introduction of intra-arterial chemotherapy for bladder cancer by Kubota in 1989, some previous studies have reported encouraging results for combined Intra-Arterial Chemotherapy for invasive or recurrent bladder cancer (Kobayashi et al. 2003; Mori et al. 2007; Miyanaga et al. 2000; Zhou et al. 2009; Zhang et al. 2016). From the collective data, we believe that NMIBC patients could also benefit from intra-arterial chemotherapy, which may be an effective treatment for preventing recurrence. In the present study, after a mean follow-up of 43.81 ± 21.43 months, patients using combined IAC treatment had a much higher recurrence-free rate (75.8%) than those in the non-IAC group (48.0%), and for the recurrent patients, a longer recurrence-free survival time was achieved (17.88 ± 12.26 vs 12.73 ± 7.56 months). High-risk NMIBC patients had the highest recurrence rate. More than half of the high-risk patients in the non-IAC group presented recurrence and the recurrence rate was in accordance with a previous study reported by Sun et al. (2017) compared to the significantly lower recurrence rate in the IAC group (26.1%). The present study was the first to compare the recurrence rate between these two groups in intermediate-risk and low-risk patients. All intermediate-risk patients with recurrence had multifocal tumors. The recurrence rate for intermediate-risk patients in the IAC group was 22.2% vs 44.4% in the non-IAC group ($p = 0.03$). Our data suggested that not only could the high-risk patients benefit from IAC, but also the intermediate-risk patients, especially those with multifocal tumors, could achieve a better outcome through IAC. None of the low-risk patients had recurrence, so it was not necessary for them to perform IAC. No CIS patients were admitted to the hospital during the research period. Consequently, the present study did not provide information about CIS cases. According to the literature, CIS is mostly multifocal and can more easily progress to muscle-invasive disease than other types of NMIBCs. There are currently no reliable prognostic factors to predict the recurrence and progression of CIS (Marko Babjuka et al. 2017).

As a novel strategy, the effectiveness of IAC is still under debate. Although demonstrated to be promising in preventing recurrence in our study, IAC failed to reduce progression significantly compared with the non-IAC group, which is inconsistent with previous findings reported by Sun et al. (2017) and Chen et al. (2013), who reported a significant decline in the progression rate. The most likely explanation for this discrepancy is the difference in enrollment of the patients recruited in the present study. In Chen's and Sun's studies, T1G3 bladder cancer and high-risk NMIBC study subjects were enrolled, while a portion of our study subjects consisted of low and intermediate-risk patients. Thus, the present study showed a lower progression rate and failed to produce significance. When examining the details of the data, almost all the cases of progression were high-risk patients with multifocal tumors, and the only intermediate-risk patient who suffered from progression also had

multifocal tumors. Moreover, the progression rate in the IAC group was extremely low, and only two patients presented progression. Our data suggest that IAC had certain advantages for those patients (intermediate and high risk) with multifocal tumors to prevent progression.

In terms of recurrence and progression, there is an urgent need to identify patients who might be candidates for IAC treatment. In our population, based on the univariate and multivariate analyses for risk factors, the number of tumors, grade and risk level were risk factors associated with recurrence. The tumor size showed no significant relation to outcomes. As is well known, TURBT plus intravesical chemotherapy is not sufficiently powerful to reduce the recurrence and progression rate in high-risk patients. In accordance with previous studies, we agree that more aggressive treatment options should be considered in high-risk patients and combined IAC would be a favorable option to conserve the bladder. For intermediate patients, the number of tumors would be an important index to discriminate candidates for IAC.

IAC has been developed to reduce systemic drug-related toxicities and to improve response rates compared with systemic chemotherapy (Han et al. 2014; Danesi et al. 2004; Azuma et al. 2010). One of the defects of IAC is that it may induce puncture-related arterial complications. Experienced interventional radiologists are required in this field to avoid arterial injury. IAC has a better safety profile and tolerability in skilled hands. No severe arterial complications were documented in our series, and only very few cases complained about puncture pain not affecting the procedure. Most drug-related side effects were gastrointestinal symptoms and hematological abnormalities. The side effects were all minor, transient and tolerable, which is consistent with previous studies (Eapen et al. 2004; Chen et al. 2013).

The limitation of the present study is the retrospective design and there might be institutional practice pattern-related bias because this was a single-institution study.

A multi-center or national randomized study in the future could overcome this advantage. Despite these limitations, the present findings suggest that IAC is a promising therapy when combined with TURBT and intravesical chemotherapy in patients with NMIBC. Especially when BCG is not available, IAC is an effective alternative to prevent recurrence and progression, thus providing the possibility for bladder preservation in patients with risk factors.

Conclusion

The present study investigated the value of IAC combined with TURBT and intravesical chemotherapy as an induction therapy for NMIBC patients. Combined IAC was found to be a promising procedure to prevent recurrence and might be useful to suppress progression. The independent risk factors for recurrence of NMIBC were multifocal tumors, grade and risk level. Intra-arterial chemotherapy was effective and safer than systemic chemotherapy. The present findings demonstrate that IAC combined with TURBT and intravesical chemotherapy provides a good alternative in patients who are intolerant to BCG or in areas where BCG is not available.

Acknowledgements The project was supported by the National Natural Science Foundation of China (no. 81102270), Guangdong Natural Science Foundation (no. 2016A030313217) and Guangdong Natural Science Foundation (no. 2016A030313206).

Author contributions FL, YW, and JL conceived and designed the research; YW and FL prepared the manuscript; LS, WC and WF collected and analyzed the data; YL and WC performed the radiologic evaluation; YL and YZ conducted the statistical analysis. All authors have read and approved the final manuscript.

Data Availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request, but no information infringing on the privacy of the participants will be provided.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the first affiliated hospital of Sun Yat-sen University (permission number: 475109).

Informed consent All participates were informed and consented to the research before they were enrolled in the study. The authors have obtained consent to publish from the participants.

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