

Definitive BCG immunotherapy versus radical cystectomy in intermediate or high-risk nonmuscle invasive bladder cancer patients

A retrospective study

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Abstract

At present, intravesical Bacillus Calmette-Guerin (BCG) immunotherapy is recommended for prophylaxis purposes after transurethral resection of bladder tumor, but has chances of recurrence. Radical cystectomy reduces the risk of recurrence in bladder cancer patients, but may have chances of postoperative complications. The objective of the study was to test the hypothesis that radical cystectomy has overtreatment and definitive BCG immunotherapy has undertreatment in intermediate or high-risk nonmuscle invasive bladder cancer patients. Data regarding biopsies, ultrasound, the computed tomography scan, adopted treatment strategy, treatment-emergent adverse effect, and a follow-up period of 312 patients with confirmed nonmuscle invasive bladder cancer (pTa, pTis, or pT1 stage; intermediate or high-risk cancer) were reviewed. Patients who had received definitive intravesical BCG immunotherapy were included in BCG group (n=210) and those who underwent radical cystectomy were included in RXC group (n=87). Clinical decision-making for treatment strategies was evaluated for both groups. Cystitis was frequently observed in all patients who received BCG immunotherapy. In RXC group, ileus was frequently observed in all patients in early days after the operation. During 2 years of the follow-up period, biopsies, ultrasound, and the computed tomography scan reported that BCG group had fewer numbers of negative cancer patients after treatment than the RXC group after surgery ($P < .0001$). Total expenditure for BCG immunotherapy was higher than radical cystectomy ($22,945 \pm 945$ ¥/patient vs $17,985 \pm 545$ ¥/patient; $P < .0001$). Definitive BCG immunotherapy had undertreatment and radical cystectomy had overtreatment for intermediate or high-risk invasive bladder cancer patients (level of evidence III).

Abbreviations: AUA = The American Urological Association, BCG = Bacillus Calmette-Guerin, CTCAE = Common Terminology Criteria for Adverse Events, DICOM = Digital Imaging and Communications in Medicine, EAU = The European Association of Urology, NCCN = The National Comprehensive Cancer Network, NICE = The National Institute for Health and Care Excellence, SUO = The Society of Urologic Oncology, USFDA = The United States Food Drug and Administration.

Keywords: bladder cancer, intravesical immunotherapy, radical cystectomy, recurrence, urological cancer

1. Introduction

Diagnosis and observation of bladder cancer is the most important medical challenge in urology practice.^[1] Bladder cancer mortality for all ages in Chinese men and women is less

than 10%,^[2] but is the most expensive malignancy to treat.^[3] Bladder cancer is mainly caused by urothelial cells' exposure to exogenous carcinogens.^[4] Nonmuscle invasive bladder cancers are mainly 3 types: the least aggressive or low-risk, moderately aggressive or intermediate-risk, and the most aggressive or high-risk.^[4] In intermediate or high-risk bladder cancer, the progression of muscle invasion, metastases, and mortality are unpredictable.^[1] There are 2 main treatment options available for intermediate or high-risk nonmuscle invasive bladder cancer: immunotherapy (intravesical Bacillus Calmette-Guerin [BCG] and removal of the bladder [radical cystectomy]).^[5] However, intravesical chemotherapy is also an available option for treatment.^[6]

Definitive BCG immunotherapy induces an immune response against the tumor and reduces the risk of malignancy progression,^[7] which do not require bladder removal. So, it may improve the quality of life of patients, but may have chances of undertreatment.^[5] A radical cystectomy removes the malignancy of bladder and adjuvant muscles.^[5] Therefore, it has best result outcomes in the patients,^[3] but may have chances of overtreatment,^[5] postoperative complications,^[8] and may reduce the quality of life of patients.^[5] At present, intravesical BCG is recommended for prophylaxis purposes after transurethral resection of bladder tumor for intermediate-risk and high-risk bladder cancer. BCG after chemotherapy has good maintenance of recurrence than radical cystectomy alone or radical cystectomy

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with chemotherapy.^[7] Therefore, to justify present treatment options, there is a need for a retrospective study before arranging a quality randomized trial.

The objective of the study was to test the hypothesis that radical cystectomy has overtreatment and definitive BCG immunotherapy has undertreatment (insufficient) for intermediate or high-risk nonmuscle invasive bladder cancer patients in a Chinese setting.

2. Materials and methods

2.1. Ethics approval and consent to participate

The protocol (ZPP/CL/2018KY232/18 dated February 1, 2018) of the study had been approved by the Zhejiang Provincial People's Hospital review board. Informed consent form was signed by all enrolled patients for participation and publication of the study during hospitalization. The study reporting adhered to the 2008 Helsinki Declaration, the strengthening and the reporting of observational studies in epidemiology (STROBE) statement, and the law of China. Registration of the study in the Chinese clinical trial registry had been waived by the institutional review board.

2.2. Inclusion criteria

Patients 18 years and above, with a confirmed (bladder tumor biopsy results; ultrasound, and the computed tomography scan confirmation) intermediate or high-risk bladder carcinoma (pTa, pTis, or pT1 stage) and advised for BCG or radical cystectomy were included in the analysis. Patients who had solely urothelial cell carcinoma or carcinoma as a major histopathological component were included in the study.

2.3. Exclusion criteria

Patients age less than 18 years, pregnant and lactating females, history of BCG treatment (for any reason), and who had not completed treatment (for any reasons) were excluded from the analysis. Patients with a confirmed (bladder tumor biopsy results; ultrasound, and the computed tomography scan confirmation) low-risk bladder cancer or absent cancer, and who were not advised for BCG treatment or radical cystectomy were excluded from the analysis.

2.4. BCG treatment

Firstly, patients were subjected to intravesical BCG immunotherapy per week for 6 weeks. Thereafter, patients were subjected to 3 doses per week of intravesical BCG immunotherapy at 4 months from the start of therapy. Lastly, patients were subjected 3 doses per week of intravesical BCG immunotherapy at 10 months from the start of therapy.^[5] After the intervention, the patients were advised to lay down on the left arm side for at least 1 hour. Urologists (minimum 3 years of experience) of the institutes performed the intravesical interventions.

2.5. Radical cystectomy

Robotic radical cystectomies had been performed by urologists (minimum 3 years of experience) of the institutes. Cystectomies were performed to remove bladder malignancies with adjacent organs (prostate and seminal vesicles in males, and the

fallopian tubes, cervix, anterior vaginal wall, and the uterus in females). The resected materials were sent to a laboratory for pathology.^[5]

2.6. Safety

During treatment and 1 year after treatment of BCG, all unexpected events were recorded. The events were considered as adverse events as per the National Cancer Institute's CTCAE (Common Terminology Criteria for Adverse Events) v5.0.^[9] Patients who faced radical cystectomies had been postoperatively followed up for 2 years, and all unexpected events during surgeries and after surgeries were recorded. The unexpected events were considered as adverse events as per the Clavien-Dindo system.^[10]

2.7. Follow-up evaluations

Biopsy, ultrasound, and the computed tomography scan were performed during the follow-up period. Ultrasound-guided biopsies and radiological evaluations were performed by physicians and radiologist (minimum 3 years of experience) of the institutes 15 days after successful treatment of BCG or radical cystectomy during the follow-up period (if further complications were noticed). If no additional compliance for urination were made by patients during the follow-up period, it was considered as no recurrence. Standard core biopsies were performed for bladder and/or surrounding tissues. The samples of biopsies were sent to a laboratory for pathology.^[11] Histopathology had been graded for high-risk, intermediate-risk, and low-risk cancer.^[4] Cancer was considered if neoplasm was in the bladder and/or surrounding tissues (eg, prostate and seminal vesicles in males, and the fallopian tubes, cervix, anterior vaginal wall, and the uterus in females). Data of morbidity were collected from the Institutes' records. Patients who underwent radical cystectomy were subjected to biopsies from surrounding tissues of the bladder.

2.8. Clinical decision-making

Clinical decision-making for therapy was evaluated for both groups as per Eq. 1:

$$\text{Beneficial score} = \frac{\text{Number of patients with no compliance for urination and negative results in biopsies}}{\text{Patients enrolled in the specific therapy}} - \left[\frac{\text{Number of patients subjected to retreatment in follow-up period}}{\text{Patients enrolled in the specific therapy}} \times \frac{\text{Threshold value}}{1 - \text{Threshold value}} \right] \quad (1)$$

2.9. Cost

Cost of diagnosis, treatment, and follow-up was calculated for each patient from DICOM (Digital Imaging and Communications in Medicine) files of the institutes and pharmacies data.

2.10. Statistical analysis

InStant GraphPad software, version window (San Diego, CA) was used for statistical analysis. Categorical data were analyzed by Fischer exact test and continuous data were analyzed by Mann-Whitney *U* test. All data were considered significant at 95% of confidence level.

3. Results

3.1. Enrollment

From July 18, 2016 to April 1, 2017, in all, 1001 patients were available at indoor patients setting of the Shidong Hospital of Yangpu District, Shanghai, China and Zhejiang Provincial People's Hospital, Hangzhou, China with complications of frequent urination, pain during urination, burning sensation during urination, hematuria, frequent urination at night, and/ or low back pain on 1 side of body. These patients were subjected to ultrasound-guided bladder biopsy, ultrasound, and the computed tomography scan. Among them, 125 patients had no cancer and 201 patients had low-risk cancer. They were excluded from the analysis. In all, 675 patients had intermediate or high-risk cancer. Among intermediate or high-risk cancer patients, 111 patients were not advised for further decided treatment. Therefore, they were excluded from the analysis. Patients who had pTa, pTis, or pT1 stage cancer were only advised for decided treatment(s). Three patients had a grade of cancer that advised for treatment, but had no sole urothelial cell carcinoma or carcinoma as a major histopathological component. Therefore, they were not subjected

for present treatment (decided for the other treatment, eg, definitive radiotherapy). One was a lactating female and 2 were pregnant females, and 1 patient had received BCG treatment in the past. Therefore, these patients were not recommended for decided treatment. In all, 312 patients were advised for treatment. Among advised patients, those who had received intravesical BCG immunotherapy were included in the BCG group and those who underwent radical cystectomy were included in RXC group. Data regarding treatment and follow-up of these patients were collected and analyzed (Fig. 1).

3.2. Demographical and clinical characters

Patients aged more than 65 years did not undergo radical cystectomy. Therefore, 225 patients had received intravesical BCG immunotherapy and 87 patients had undergone radical cystectomy. Among them, 15 patients had not completed BCG treatment. Therefore, data of these patients were excluded from the analysis. For sociological, economical, demographical, and clinical characteristics of the enrolled patients, there were no significant differences between both groups ($P > .05$ for all) except age (Table 1).

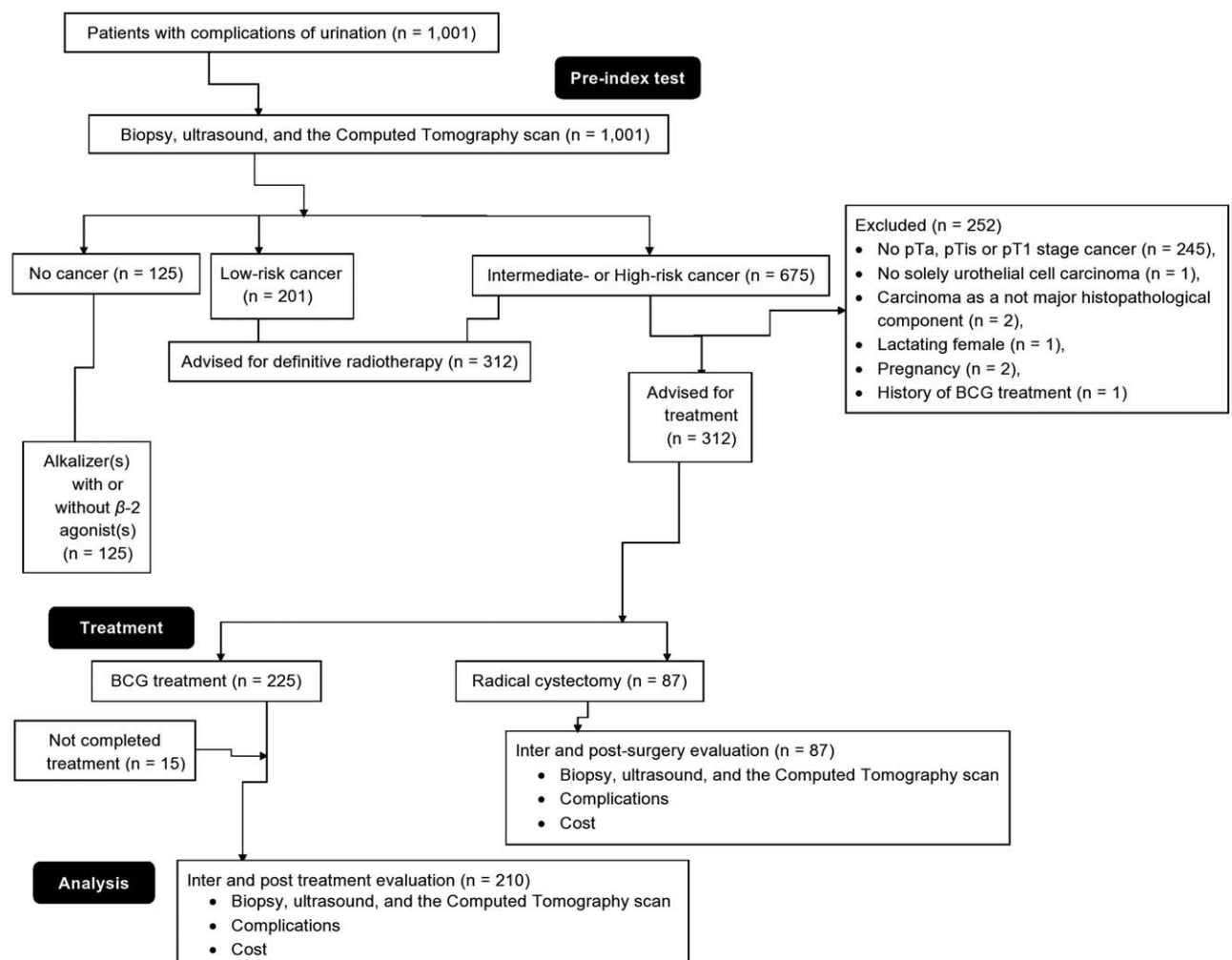


Figure 1. Flowchart of analysis.

Table 1**Sociological, economical, demographical, and clinical characteristics of the enrolled patients.**

Parameters	Group		Comparisons between groups <i>P</i>
	BCG 210	RXC 87	
Patients enrolled (sample size)			
Age			
Maximum	75	65	<.0001
Minimum	18	18	
Mean ± SD	66.15 ± 7.15*	56.85 ± 5.45	
Sex			
Male	167 (80)	66 (76)	.536
Female	43 (20)	21 (24)	
Ethnicity			
Han Chinese	179 (85)	79 (91)	.424
Mongolian	28 (13)	7 (8)	
Tibetan	3 (2)	1 (1)	
Economic status			
High income	43 (20)	15 (17)	.811
Medium income	66 (32)	28 (32)	
Low income	101 (48)	44 (51)	
Smoker			
No smoker	140 (66)	46 (53)	.073
Previous smoker	54 (26)	30 (34)	
Current smoker	16 (8)	11 (13)	
Cancer stage			
pTa	66 (31)	29 (33)	.246
pTis	61 (29)	32 (37)	
pT1	83 (40)	26 (30)	
Bladder tumor biopsy results			
Solely urothelial cell carcinoma	101 (48)	41 (47)	.899
Carcinoma as a major histopathological component	109 (52)	46 (53)	
Body mass index (kg/m ²)			
19.5–24.9 (normal)	101 (48)	45 (52)	.684
25–29.9 (obese)	86 (41)	31 (36)	
≥30 (overweight)	23 (11)	11 (13)	

Constant variables were represented as frequency (percentage) and continuous variables were represented as mean ± SD.

Fischer exact test was used for constant variables and Mann-Whitney *U* test was used for continuous variables.

A *P* < .05 was considered significant.

* Significant higher for BCG group.

3.3. Noncancerous adverse events

Cystitis was frequently observed in all patients who received BCG immunotherapy. Patients were put on rifampicin and isoniazid until the treatment was completed in such complications. Oral paracetamol was given in cases of fever. The extra-urinary complications were very often. In the RXC group, ileus was

frequently observed in all patients in early days after the operation. Patients were put on a soft diet for 3 days after radical cystectomy. Fewer numbers of patients of the RXC group had reported hematuria than those in the BCG group (35 vs 2; *P* = .0003). No neurological and cardiological adverse effects were reported in both groups (Table 2).

Table 2**Adverse effects during the follow-up period.**

Adverse effects	BCG group	Adverse effects	RXC group
Patients enrolled (sample size)	210	Patients enrolled (sample size)	87
Cystitis	199 (95)	Constipation	8 (9)
Hematuria	35 (17)	Urosepsis	7 (8)
Dysuria	2 (1)	Symptomatic urinary leakage	2 (2)
Bladder contracture	2 (1)	Ileus	20 (23)
Acute fever	39 (19)	Urinary retention	2 (3)
Weight loss	2 (1)	Hematuria	2 (3)
High erythrocyte sedimentation rate*	40 (19)	Emesis	2 (3)

Data are represented as frequency (percentage).

* The normal range: 0–22 mm/h for men and 0–29 mm/h for women.

Table 3
The follow-up evaluations.

Parameters	Group		Comparisons between groups <i>P</i>
	BCG 210	RXC 87	
Patients enrolled in the specific therapy (sample size)			
No cancer*	87 (41)	58 (67)	<0.0001
Low-risk cancer	54 (26)	12 (14)	0.031
Medium-risk cancer	37 (18)	8 (9) [†]	0.076
High-risk cancer	32 (15)	9 (10) [†]	0.467
Patients subjected to retreatment [‡]	25 (12)	8 (9) [†]	0.435

Cancer indicates neoplasm in the bladder or surrounding tissues (eg, prostate and seminal vesicles in males, and the fallopian tubes, cervix, anterior vaginal wall, and the uterus in females).

Constant variables are represented as frequency (percentage) and continuous variables were represented as mean ± SD.

Fischer exact test was used for constant variables and Mann-Whitney *U* test was used for continuous variables.

A *P* < .05 was considered significant.

* No compliance for urination was made by patients or negative results in a biopsy, ultrasound, and the computed tomography scan.

[†] Insignificant difference with respect to BCG group.

[‡] In BCG group retreatment with weekly BCG immunotherapy for 3 weeks, and in RXC group extra oophorectomy or pelvic lymphadenectomy, or any chemotherapeutic treatment.

3.4. Cancerous adverse events

During 2 years of the follow-up period, postoperative biopsy reported that BCG group had fewer numbers of negative cancers patients after treatment than RXC group after surgery (*P* < .0001), but high numbers of low-risk patients than RXC group after surgery (*P* = .031). The same numbers of patients with medium risk (*P* = .076), high risk (*P* = .467), and retreatment (*P* = .435) of cancer for bladder or any the other part of the body were reported by both groups (Table 3).

3.5. Clinical decision-making

Level of confidence for clinical decision-making of treatment reported that BCG immunotherapy had undertreatment

and radical cystectomy had overtreatment for a patient with intermediate or high-risk bladder cancer. Among the radical cystectomies, those performed by 3 to 4 years of experienced urologists had a high level of enthusiasm, but had a high risk of postoperative complications (Fig. 2).

3.6. Cost

Total expenditure for BCG immunotherapy was higher than radical cystectomy (22,945 ± 945 ¥/patient vs 17,985 ± 545 ¥/patient; *P* < .0001; Fig. 3).

During the follow-up period of 2 years, only 1 patient died from the BCG group.

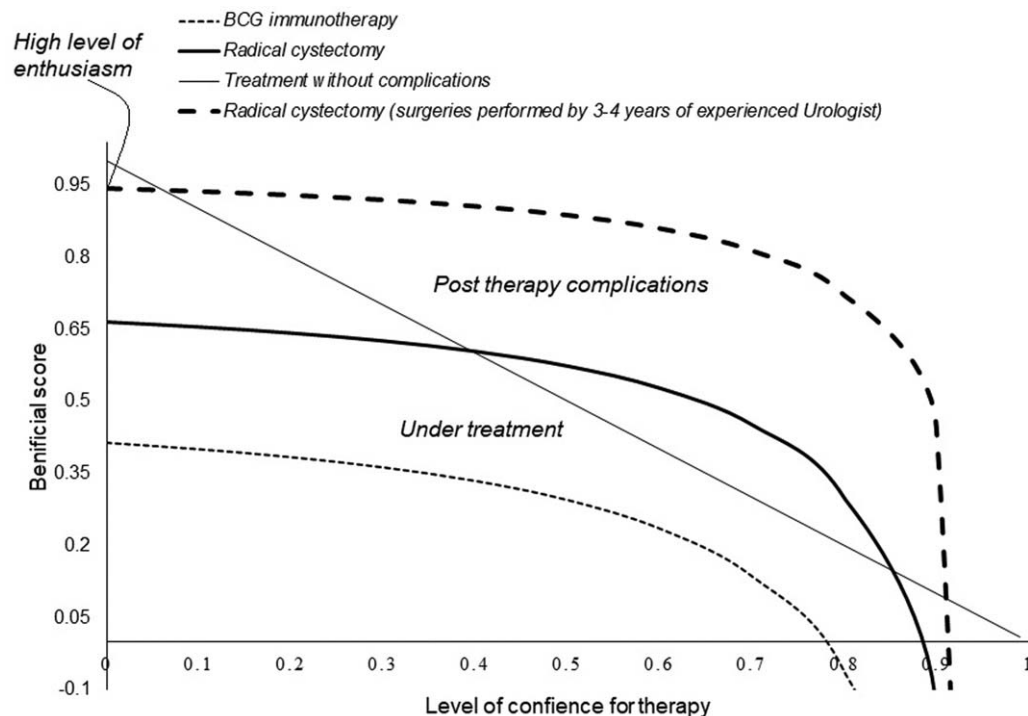


Figure 2. Clinical decision-making for therapy. Cancer indicates neoplasm in the bladder or surrounding tissues (eg, prostate and seminal vesicles in males, and the fallopian tubes, cervix, anterior vaginal wall, and the uterus in females) in a biopsy, ultrasound, and the computed tomography scan.

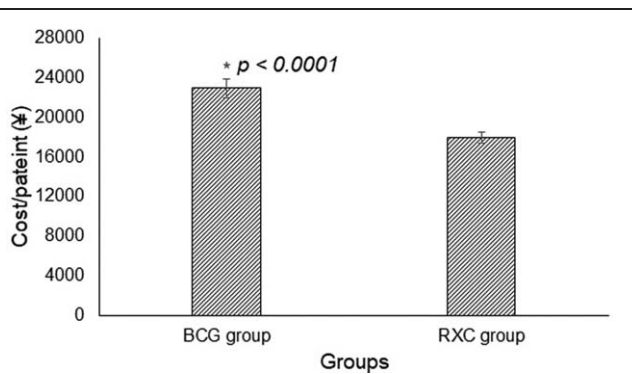


Figure 3. Expenditure on therapy. * Significant higher cost. Mann-Whitney *U* test was used for statistical analysis. A $P < .05$ was considered significant. In all, 210 patients from BCG and 87 patients from RXC group were used in the analysis. Data were represented as mean \pm SD.

4. Discussion

4.1. Treatment options

The study is the first retrospective study that reported a comparison of definitive BCG immunotherapy against radical cystectomy in nonmuscle invasive intermediate or high-risk bladder cancer patients. BCG is approved by the United States Food Drug and Administration (USFDA) in 1990.^[7] The American Urological Association (AUA)/the Society of Urologic Oncology (SUO) guidelines,^[12] the European Association of Urology (EAU) guideline,^[4] the National Comprehensive Cancer Network (NCCN) guideline,^[13] and the National Institute for Health and Care Excellence (NICE) guidelines^[14] for the intermediate or high-risk bladder cancer recommended transurethral resection followed by maintenance dose of intravesical BCG immunotherapy. Both combining treatments have high cost^[15] and also have treatment-emergent adverse effects^[8,16] and risk of recurrence. Therefore, treatments recommended by these present guidelines have the risk of financial burden over patients' head and high morbidities.

4.2. Adverse effects

Cystitis was frequently observed due to BCG immunotherapy, and ileus was commonly found due to radical cystectomy. The results of the study were in line with available studies.^[8,16] Experienced surgeons can reduce complications due to radical cystectomy, whereas rifampicin and other drugs would be used to manage adverse effects due to BCG treatment. Appropriate treatment with measures to overcome complications is recommended in intermediate or high-risk bladder cancer.

4.3. Recurrence

During 2 years of follow-up, 59% of patients who were treated with BCG immunotherapy developed recurrence. Presumably, recurrences in patients treated with BCG should be within the bladder and less likely to be metastatic. Recurrences in patients who have undergone cystectomy should be overall more severe, because they will recur outside of the bladder (meaning they either are recurring in their upper tracts or there is metastasis). The results of recurrence of the study were higher than the retrospective, nonrandomized study^[17] and randomized pro-

spective trial,^[18] because in the current study, definitive BCG immunotherapy was used instead of maintenance therapy. However, the results were consistent with the results of a retrospective study.^[19] Definitive BCG immunotherapy has the issue of undertreatment because it is self-evident that only patients with a bladder will be able to experience bladder recurrence or bladder symptoms.

The treatment cost of radical cystectomy is competitive, and during 2 years of follow-up, only 33% of patients developed recurrence, but ileus, constipation, urosepsis, and other complications after radical cystectomy were frequent. Recurrence rate seems very high for nonmuscle invasive bladder cancer. The possible reasons for this recurrence were a delay in surgeries.^[6,19] The results of the study were in line with the retrospective studies.^[6,8] The radical cystectomy has the issue of overtreatment.

4.4. Limitations

Despite a large number of bladder cancers patients enrolled in the study, several limitations of the study have been reported, for example, only retrospective data review subjected to selection bias, lack of nonrandomized trial with careful initial cancer staging. The possible justification for the surgeries is difficult to compare with the treatment in a nonrandomized trial. In bladder cancer, for significance comparisons of recurrence and death, 10 to 15 years of follow-up time is required,^[18] but the survival of patients was reported for 2 years only. A possible justification for the short-term follow-up is that crossover phenomenon has resulted in long-term follow-up times leads to confounding effects on results^[7] and creates a dilemma in the selection of treatment (s). The absence of standard chemotherapy treatment (control group) for comparison purpose. Cystectomies for patients aged more than 65 years were not performed, and reasons for such exclusions were not reported. The BCG group and RXC group are significantly different based on age ($P < .0001$).

5. Conclusions

Definitive BCG immunotherapy and radical cystectomy both were effective in nonmuscle invasive intermediate or high-risk bladder cancer, but definitive BCG immunotherapy had a risk of undertreatment and the high cost of therapy, whereas radical cystectomy had a risk of overtreatment. Dose and dosage forms of BCG immunotherapy are required to amend the guidelines to get proper treatment, and experienced urologists can decrease the risk of overtreatment of radical cystectomy. The large human nonrandomized trial is recommended.

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Supervision: Guodong Jian.

Validation: Xiaoming Jian.

Writing – original draft: Guodong Liao.

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