


ORIGINAL RESEARCH

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Comparison of the efficacy of BCG intravesical immunotherapy using the conventional Rotisserie method with the non-Rotisserie method

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Abstract

Background Intravesical BCG injections are administered following transurethral resection of the superficial bladder tumor in order to increase the success rate and decrease the risk of tumor recurrence. BCG therapy has been examined extensively in terms of dosage and injection time intervals to determine its effectiveness. However, no study has yet been conducted to compare the two qualitatively different methods of administering BCG (Rotisserie and non-Rotisserie).

Methods This study included 30 patients with non-muscle-invasive bladder TCC, whose tumor stage was Ta or T1. Two groups of 15 patients were randomly selected. The first intravesical injection of BCG was administered 2 weeks following transurethral resection of the bladder tumor and then continued as the maintenance treatment. But, in one group, the injection was done by Rotisserie method, and in the other group, non-Rotisserie method was performed. Then, the patients underwent periodic follow-up by cystoscopy to determine if recurrences had occurred.

Results A total of 23 participants (76.66%) were males, while seven patients (23.34%) were females. There were 20 participants (66.66%) with tumors in the Ta stage and ten participants (33.34%) with tumors in the T1 stage. There were 22 patients (73.3%) with low-grade tumors and eight (26.7%) with high-grade tumors. Five participants (16.66%) experienced tumor recurrence during the study, three of whom were in the Rotisserie group and two in the Non-Rotisserie group. In terms of preventing tumor recurrence, there were no significant differences between Rotisserie and non-Rotisserie methods (P value = 0.6).

Conclusion Due to the lack of significant difference in the rate of tumor recurrence between the two methods of intravesical BCG injection (Rotisserie and non-Rotisserie), it is not necessary to rotate the patients after BCG injection. This will also allow patients to be discharged from the hospital earlier and reduce the likelihood of complications.

Keywords Bladder cancer, BCG, Immunotherapy, Rotisserie, Non-Rotisserie

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1 Background

Globally, bladder cancer affects approximately 430,000 people each year, which this making it the most common malignancy of the urinary system [1, 2]. It has a wide range of severity, from slow-progressing low-grade Ta tumors to malignant high-grade tumors, with a mortality rate exceeding 145,000 per year [2, 3]. About 70% of bladder cancer cases are caused by superficial TCC, 70% of which are Ta types, 20% are T1 types, and 10% are carcinomas *in situ*. The survival rate for muscle-invasive bladder cancer has remained relatively constant in the past 18 years, and with treatment, the 5-year survival rate has been 50% [4].

This survival rate for metastatic bladder cancer is only 15% [5, 6]. Studies have proven that smoking and occupational exposure to urothelial carcinogens are the two most prominent risk factors for bladder cancer [3]. It has also been demonstrated that bladder cancer is immunogenic, as the PD-1 transmembrane protein expressed on the surface of cytotoxic T cells bound to the PDL-1 receptor present on the surface of cancer cells, and this leads to a decrease in the host's immunity against cancer. In this way, using PD-1/PDL-1 inhibitors can increase the body's immune response to tumor cells [7, 8]. The immunotherapy method has revolutionized the treatment of many cancers, including melanoma and kidney cancer [8, 9]. The attenuated strain of *Mycobacterium bovis* or Bacillus Calmette–Guérin (BCG) was used by Zbar et al. to induce antitumor effects and by Morales et al. for the intravesical treatment of non-muscle-invasive bladder cancer [10, 11]. Currently, BCG is the most effective immunotherapy method available for the treatment of non-muscle-invasive bladder TCC (Ta, T1, and carcinoma *in situ*). It provides greater therapeutic benefits than intravesical chemotherapy [12, 13]. The mechanism by which BCG works is not well understood. The strong increase in urinary cytokines following the intravesical injection suggests that BCG inhibits tumor growth by triggering the immune system [14, 15]. It is also stated in other studies that this treatment method is more successful in the prevention of tumor recurrence, than intravesical chemotherapy regimens. It also reduces the possibility of tumor progression, which this effect is not seen in intravesical chemotherapy [16]. Despite its therapeutic benefits, this method can result in some adverse effects, including local irritation, fever, general weakness, and sepsis. Consequently, it is prohibited to perform in patients with gross hematuria and severe urinary tract inflammation [17]. Depending on the urologist's preference, intravesical injection of BCG is performed in one of these two ways; in the conventional method, known as Rotisserie, after intravesical injection of BCG, the patient lies on his back, and then in 15-min intervals, he

changes his position to lying on his sides and stomach [18]. In another way, we call it non-Rotisserie, patient is discharged in a short period of time after the injection, without being placed in different positions.

Even though most urologists recommend turning the patient in different directions following BCG injection to ensure that the entire surface of the urothelium is in contact with BCG, there is no scientific support for acting according to this method [19, 20].

Shah et al. stated that since the bladder due to its flexible nature changes its size according to the volume of liquid that enters it, the Rotisserie method has no scientific basis and except for cases where a large air bubble has entered the bladder due to wrong injection, it is not necessary to rotate the patient serially [21].

This study aims to compare the effectiveness of intravesical BCG injection using the conventional Rotisserie method with the non-Rotisserie method. The results can, therefore, assist in determining the most effective method for intravesical BCG injections.

2 Methods

This longitudinal-descriptive study was conducted from March 2019 to February 2020 on patients with bladder cancer who were referred to the urology clinic of Valiasr Hospital, Qaemshahr, Iran. Upon confirmation of the diagnosis with cystoscopy, all patients underwent transurethral resection of the bladder tumor by a predetermined urologist. Ultimately, 30 patients with non-muscle-invasive bladder TCC were included in the study. There were three pathological features: high-grade Ta, low-grade T1, and high-grade T1. Intravesical BCG injections were administered 2 weeks after TURBT, initially as an induction treatment and then as a maintenance treatment.

The induction regimen consisted of 6 weekly injections, and the maintenance regimen was based on SWOG (southwest oncology group) method. Accordingly, three doses of BCG were prescribed weekly in months 3–6–12–18–24–30–36. One vial of 120 mg of BCG (the strain of Iran Pasteur Institute) is suspended in 50 mL of normal saline and then injected into the bladder via the urethral catheter. The agent should be retained in the bladder for at least 2 hours and then voided [19]. BCG injections were performed using two different methods (Rotisserie vs non-Rotisserie). The Rotisserie method involves placing the patient in a supine position after an intravesical injection and then changing the position at 15-min intervals to the left flank up, the right flank up, and prone. In the non-Rotisserie method, the patient is discharged shortly after injection without being placed in different positions [18]. Two groups of 15 patients were randomly selected. Participants were randomly assigned

to either the Rotisserie or non-Rotisserie group using a random number table. BCG injection was performed using the Rotisserie method in the first group and the non-Rotisserie method in the second group. Demographic data, including age, gender, tumor histopathology, cystoscopy data, and the number of BCG injections, were collected and compiled. A follow-up cystoscopy was performed every 3 months for 1 year. This study included patients with non-muscle-invasive bladder tumors who had no contraindications to receive intravesical injections. Exclusion criteria were immunosuppression, a history of BCG sepsis, gross hematuria or traumatic catheterization, and active urinary tract infections. Data collected were analyzed using SPSS software version 26. Quantitative results were described using central and dispersion statistics. Quantitative data were also described as absolute and relative frequencies. Written informed consent was obtained from all subjects before the study. The study protocol was approved by the ethics committee of Sari University of Medical Sciences (IRB Number: IR.IAU.SARI.REC.1399.035).

3 Results

The study involved 30 patients, of which 23 were men (76.66%) and 7 were women (23.34%). A total of six individuals (20%) were less than 45 years of age, eight individuals (26.7%) were between 45 and 60 years of age, and 16 individuals (53.3 percent) were over 60 years of age. Twenty participants had a tumor in stage Ta (66.66%) and ten participants had a tumor in stage T1 (33.34%). Eight patients (26.7%) had high-grade tumors, and 22 patients (73.3%) had low-grade tumors. Among the participants, 16 (53.3%) had only one tumor, while 14 (46.7%) had two or more tumors. Five patients (16.66%) experienced tumor recurrence during the study, out of which three were in the Rotisserie group and two were in the non-Rotisserie group. In terms of preventing tumor recurrence, there were no significant differences between Rotisserie and non-Rotisserie methods (P value=0.6) (Table 1).

4 Discussion

Bladder cancer is the eighth leading cause of death due to cancer and represents 3% of all cancers [22–24]. There is an increase in the incidence of this cancer in Iran [22]. In order to maximize the success rate of the transurethral resection of superficial bladder tumor, various agents are usually injected intravesically to reduce the possibility of recurrence. Currently, intravesical BCG therapy is the most effective immunotherapy method available for the treatment of non-muscle-invasive bladder tumors (Ta, T1, and carcinoma *in situ*). It provides greater therapeutic benefits than intravesical chemotherapy since it

Table 1 Inter-pattern analyze of tumor recurrence

	N (%)	P value
<i>Gender</i>		
Male	23 (76.6)	0.19
Female	7 (23.3)	
<i>Age (years)</i>		
< 45	6 (20)	2.1
45–60	8 (26.7)	
> 60	16 (53.3)	
<i>Injection method</i>		
Rotisserie group	3 (20)	0.6
Non-Rotisserie group	2 (13.3)	
<i>Tumor grade</i>		
Low grade	22 (73.3)	0.09
High grade	8 (26.7)	
<i>Tumor stage</i>		
Ta	20 (66.6)	0.02
T1	10 (33.3)	

reduces the likelihood of both tumor recurrence and tumor progression [12, 13].

Several studies have been conducted to assess the effectiveness of different approaches to intravesical BCG therapy in terms of dosage and sequence of injections; our study is the first to compare the two qualitatively different BCG injection methods (Rotisserie and non-Rotisserie). The majority of our patients (76.66%) were males, which was consistent with global bladder cancer statistics. In the study by Racioppi et al. [25], 82.5% of the participants were men. Patients in our study ranged in age from 24 to 84 years, with a mean age of 57 years. According to Ghazi Moghadam et al.'s study, the patients' ages ranged between 37 and 84 years, with a mean age of 61 years [26]. It has also been reported that the highest prevalence of bladder tumors occurred in the seventh and eighth decades with an average age of 66 years old [27]. A total of five patients had tumor recurrence during the course of this study, of whom three were in the Rotisserie group, but no significant difference was observed between the Rotisserie and non-Rotisserie groups in terms of tumor recurrence (P value=0.666). There has been no similar study conducted to evaluate the effectiveness of the two methods discussed above. Approximately two-thirds of the patients in our study had tumors in the Ta stage, and the remainder had tumors in the T1 stage. As in our study, Ghazi Moghadam et al. [24] reported that approximately 56% of their patients had Ta tumors. In our research, the most cases of recurrence were related to T1 stage and statistical analysis, showed a significant relationship between T1 stage and tumor recurrence (P value=0.020). As well, Tadayon et al.

[28] reported a significant relationship between bladder tumor T stage and tumor recurrence, so that most cases of recurrence were from T1 stage (P value = 0.006). In our study, no statistically significant difference was observed between tumor grade and tumor recurrence. Also, the studies conducted by Tadayon et al. and Racioppi et al. [25, 28] did not show a significant correlation between tumor grade and tumor recurrence.

This study has the advantage of being the first to assess and compare two methods of injecting BCG. In order to provide a better understanding of the subject, however, studies with larger sample sizes and longer follow-up periods are recommended in order to obtain a better understanding of the topic. In addition, to gain a comprehensive understanding of the issue, it is crucial that research is conducted on a variety of age groups and populations.

5 Conclusion

According to our results, the Rotisserie method does not significantly differ from non-Rotisserie methods in terms of tumor recurrence. Therefore, it is not necessary to turn the patient in different directions after the BCG injection. The patient can be discharged immediately after injection. It may result in fewer hospital complications for the patients, however, given the limited number of studies conducted in this field and the limited number of participants in this study, further research is required in the future to obtain more accurate results.

Abbreviations

BCG Bacillus Calmette–Guérin
TCC Transitional cell carcinoma

Acknowledgements

None.

Author contributions

MKH and MBR worked in project development, supervision, and review and editing manuscript. BN worked in supervision, review and editing manuscript, data collection, and management. SR contributed to writing and editing original draft, data collection, and management. GR contributed to writing and editing original draft, analysis and interpretation of data, data collection, and management. MA contributed to writing and editing original draft, analysis and interpretation of data, data collection, and management.

Funding

None.

Availability of data and materials

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate

All procedures involving human participants in the study were approved by the Ethics Committee of the SARI University of Medical Sciences with the

number IR.IAU.SARI.REC.1399.035. Written informed consent was obtained from all subjects before the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Received: 10 February 2023 Accepted: 28 August 2023

Published online: 12 October 2023

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