ORIGINAL RESEARCH

DOI: 10.37047/jos.2022-91733

Intravesical Bacillus Calmette-Guérin Reduces Lung Involvement in COVID-19 in Patients with Bladder Cancer

Mehmet Serkan ÖZKENT[a], Yunus Emre GÖGER[b], Nurullah ALTINKAYA[b], Mehmet ARTAÇ[c]

aClinic of Urology, Konya City Hospital, Konya, Türkiye
bDepartment of Urology, Necmettin Erbakan University Meram Faculty of Medicine, Konya, Türkiye
cDivision of Medical Oncology, Necmettin Erbakan University Meram Faculty of Medicine, Konya, Türkiye

ABSTRACT Objective: To compare the coronavirus disease-19 (COVID-19) infection, morbidity, and mortality rates of patients who did not receive and received Bacillus Calmette-Guérin (BCG) treatment because of bladder cancer during the COVID-19 pandemic. **Material and Methods:** Patients who were followed up for bladder cancer between March 2019 and March 2021 were evaluated. Patients who underwent intravesical BCG instillation (induction or maintenance) and those who did not receive BCG were divided into two groups. The characteristics (age, gender, etc.) and COVID-19-related findings (symptoms, comorbidities, lung involvement, and need for patient admission) of the patients were recorded and compared between the groups. **Results:** The present study included 215 patients (85 in Group 1; and 130 in Group 2). Demographic data were similar in both groups (body mass index, age, gender, comorbidities, etc.). COVID-19 incidence was similar in both groups (18 patients in Group 1; 21 patients in Group 2; p: 0.350). The number of patients with COVID-19 treated in the hospital was more in Group 1 than in Group 2 (14 patients in Group 1, 7 patients in Group 2, p: 0.006). However, lung involvement and dyspnea were significantly lower in the intravesical BCG Group (p: 0.015; and p: 0.001, respectively). **Conclusion:** Intravesical BCG instillation reduces the morbidity associated with COVID-19. Therefore, the installation schemes should not be delayed due to the pandemic. The current study imparts preliminary information about the importance of BCG vaccination studies against COVID-19.

Keywords: Bladder cancer; COVID-19; intravesical Bacillus Calmette-Guérin; non-invasive bladder tumor; lung involvement; morbidity of COVID-19

The coronavirus disease-19 (COVID-19) is a new form of respiratory tract infection further complicated by severe pneumonia and acute respiratory distress syndrome. On February 11, 2020, a newly identified viral pathogen called severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was identified to cause severe acute respiratory syndrome.[1] The person infected with SARS-CoV-2 remains asymptomatic or develops a mild to moderate illness mainly characterized by respiratory symptoms. It has a mortal course, especially in the elderly, cancer patients, immunosuppressed patients, and people from a lower socioeconomic status or with inadequate health systems.[2-4] The pathogenesis of the disease probably involves initiating an immune response.[5] The virus attaches to the angiotensin-converting enzyme-2 (ACE-2) with its spike protein. The viral RNA undergoes replication and transcription after the viral and plasma membranes fuse. These events initiate a series of inflammatory processes. The "cytokine storm" resulting from the cytokines released via different receptors causes tissue damage in the host. The inflammation involves the healthy pulmonary tissue of the host, thus, leading to respiratory failure and related mortality.[5]

Bacillus Calmette-Guérin (BCG) is a vaccine administered since the 20th century to neonates and infants to prevent tuberculous meningitis and disseminated tuberculosis.[6] Most notably, BCG vaccination of neonates decreases overall childhood

Correspondence: Mehmet Serkan ÖZKENT
Clinic of Urology, Konya City Hospital, Konya, Türkiye
E-mail: msozkent@gmail.com

Peer review under responsibility of Journal of Oncological Sciences.

Received: 03 Jun 2022 ***Received in revised form:*** 11 Oct 2022 ***Accepted:*** 13 Oct 2022 ***Available online:*** 07 Nov 2022

mortality, including mortality unrelated to tuberculosis, mainly driven by a decrease in sepsis and respiratory infections in childhood.[7,8] BCG reduces the risk of many viral infections such as respiratory syncytial virus (RSV), yellow fever disease, and herpes simplex virus (HSV) Type 2.[7-10] Some studies identified the benefits of BCG in cellular and molecular response mechanisms.[9] The relationship between the BCG vaccine and the clinical course of COVID-19 is controversial. However, the heterogeneous contributions of BCG to immunity cannot be denied. Clinical studies on the BCG vaccine and COVID-19 have been initiated.[11]

In urology, BCG is an intravesical treatment used for a long time in non-muscle invasive bladder cancers (NMIBC). The European Association of Urology (EAU) and American Urological Association recommend using BCG in treating medium and high-risk bladder cancer since it prevents progression and recurrence.[12,13] However, the underlying mechanisms are not entirely understood. BCG also exerts its anti-tumor activity by stimulating urothelial cells and the immune system. Studies have shown that local BCG stimulates a systemic immune response.[14,15]

According to the relevant literature, BCG does not protect directly against coronavirus but boosts the immune system, causing improved protection and a milder infection.[10,16,17] These reports raise questions about the effect of intravesical BCG application on COVID-19 patients. Hence, the present study was designed to compare COVID-19 infection, morbidity, and mortality rates of patients who received BCG treatment because of bladder cancer and those who did not receive it during the COVID-19 pandemic.

MATERIAL AND METHODS

A university hospital urology department and a city hospital urology clinic were identified for screening the patients. The patients who had undergone transurethral resection-bladder and were diagnosed with NMIBC between March 11, 2019, and March 11, 2021, in the aftermath of the first COVID-19 case in our country, were considered. The files of these patients were analyzed retrospectively.

The patients were classified following EAU guidelines according to their risk groups, and treatment and follow-up protocols were formed.[12] Patients were divided into two groups: Group 1 included those patients who did not receive intravesical BCG therapy. Group 2 included patients who received at least six cycles of maintenance intravesical BCG treatment, were currently on full-dose intravesical therapy or had completed the full-dose intravesical BCG therapy within the last three months.

Patients with muscle-invasive bladder cancer pathology, or those who discontinued their follow-up, refused to participate in the present study, did not continue intravesical BCG treatment, and did not complete at least six weeks of intravesical BCG induction, were excluded from the study.

Data of the patients (age, gender, pathology, intravesical BCG therapy, etc.) were recorded. In addition, the COVID-19 infection and related findings (symptoms, comorbidities, lung involvement, and need for patient admission) of these patients during this period were recorded and compared between the groups.

ETHICAL 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 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The analysis and data collection were performed following the after written informed consent was obtained from all patients. The institutional human research ethics committee approved (Necmettin Erbakan University, Meram Medical Faculty Ethics Committee, date: April 16, 2021, protocol number: 2021/3194).

STATISTICAL ANALYSES

The data and results of the patients were compared using the SPSS Statistics 22.0 software (SPSS Inc., Chicago, IL, USA). The skewness and kurtosis tests were performed to ensure the normal distribution of the data. Independent t-tests, Mann-Whitney tests, and chi-square tests were used for comparative analysis. Statistical significance was determined at a 95% confidence interval and $p<0.05$.

RESULTS

The study included 215 patients. Among these, 85 (39.5%) belonged to Group 1 and 130 (60.5%) to Group 2. Female patients contributed 19.1% (41), and male patients contributed 80.9% (174). The mean patient age was similar (63.7±10.5 years) in both groups (independent t-test, p: 0.344); 64.6±9.4 years in Group 1, and 63.2±11.1 years in Group 2. The mean body mass index of the patients was similar in both groups (27.5±2.5 kg/m^2 in Group 1 and 27.2±3.1 kg/m^2 in Group 2; independent t-test, p: 0.452) (Table 1).

Of the 215 patients, 87 (40.5%) had one comorbidity, and 58 (27%) had more than one comorbidity. Further, 62 patients (72.9%) in Group 1 and 83 (63.8%) in Group 2 had at least one comorbidity. The most prevalent comorbidities were hypertension (73 patients, 34%) and diabetes (47 patients, 21.9%). This was followed by cardiovascular disease (43 patients, 20%), respiratory system disease (25 patients, 11.6%), cancer (4 patients, 1.9%) and others (60 patients, 27.9%, liver disease, psychiatric disorders, gastrointestinal disorders, rheumatological diseases, etc.). The presence of comorbidity was similar between the groups (chi-square; p: 0.182).

Moreover, eighteen of the patients (21.2%) in Group 1 and 21 (16.2%) in Group 2 were diagnosed with COVID-19. COVID-19 incidence was similar in both groups (chi-square; p: 0.350). Twenty-one (53.8%) patients diagnosed with COVID-19 were treated in a hospital. The number of patients was more in Group 1 (14 patients in Group 1, 17.5%; 7 patients in Group 2, 5.4%; chi-square; p: 0.006).

The most prevalent clinical symptom was fever (30 patients, 76.9%), followed by cough (28, 71.8%), dyspnea (24, 61.5%), fatigue (21, 53.8%), and others (10, 25.6%). Pulmonary involvement was observed in 20 patients (51.3%). In addition, three (7.7%) patients died due to COVID-19. The ratios of symptoms, comorbidities, and deaths were similar between the groups (Fisher's exact test: p: 0.464 for fever; p: 0.134 for cough; p: 0.486 for fatigue; p: 0.856 for others; and p: 0.182 for comorbidities) (Table 2). However, lung involvement and dyspnea were significantly lower in the intravesical BCG Group (chi-square, p: 0.015; and p: 0.001, respectively) (Figure 1).

DISCUSSION

The data for the present study were collected from the records of the patients treated in two tertiary medical centers of the region. These centers have conducted active uro-oncological interventions since the outbreak of the pandemic. Hence, the diagnosis and treatment protocol of most bladder cancer patients in the region were arranged in these two centers. In the present study, a statistically significant difference was

TABLE 1: Demographic characteristics of patients in both groups.

Variables	Group 1	Group 2	p val-ue
Patients (n)	85	130	
Patients' age (years) (X±SD)	64.6±9.4	63.2±11.1	0.344
BMI of patients (kg/m2) (X±SD)	27.5±2.5	27.2±3.1	0.452
The patients with COVID-19 (n) (%)	18 (21.2%)	21 (16.2%)	0.350
Comorbidities (n) (%)	62 (72.9%)	83 (63.8%)	0.182
One comorbidity	31 (36.5%)	56 (43.1%)	0.171
More than one comorbidity	31 (36.5%)	27 (20.8%)	0.171
HT	27 (31.8%)	46 (35.4%)	
DM	23 (27.1%)	24 (18.5%)	
Cardiovascular disease	22 (25.9%)	21 (16.2%)	
Respiratory system disease	10 (11.8%)	15 (11.5%)	
Others (liver disease, psychiatric disorders, GI disorders, etc.)	31 (36.4%)	29 (22.3%)	

SD: Standard deviation; BMI: Body mass index; HT: Hypertension; DM: Diabetes mellitus; GI: Gastrointestinal.

TABLE 2: Comparison of the findings of patients with COVID-19 by chi-square.

	Group 1	Group 2	p value
COVID-19 (n) (%)	18 (21.2%)	21 (16.2%)	0.350
Hospitalization (n) (%)	14 (17.5%)	7 (5.4%)	0.006
Fever (n) (%)	15 (17.6%)	15 (11.5%)	0.464
Cough	13 (15.3%)	15 (11.5%)	0.634
Dyspnea	16 (18.8%)	8 (6.2%)	0.001
Fatigue	10 (11.8%)	11 (8.5%)	0.486
Others	4 (4.7%)	6 (4.6%)	0.856
Pulmonary involvement (n) (%)	10 (11.8%)	5 (3.8%)	0.014
Ex (n) (%)	2 (2.4%)	1 (0.8%)	0.422

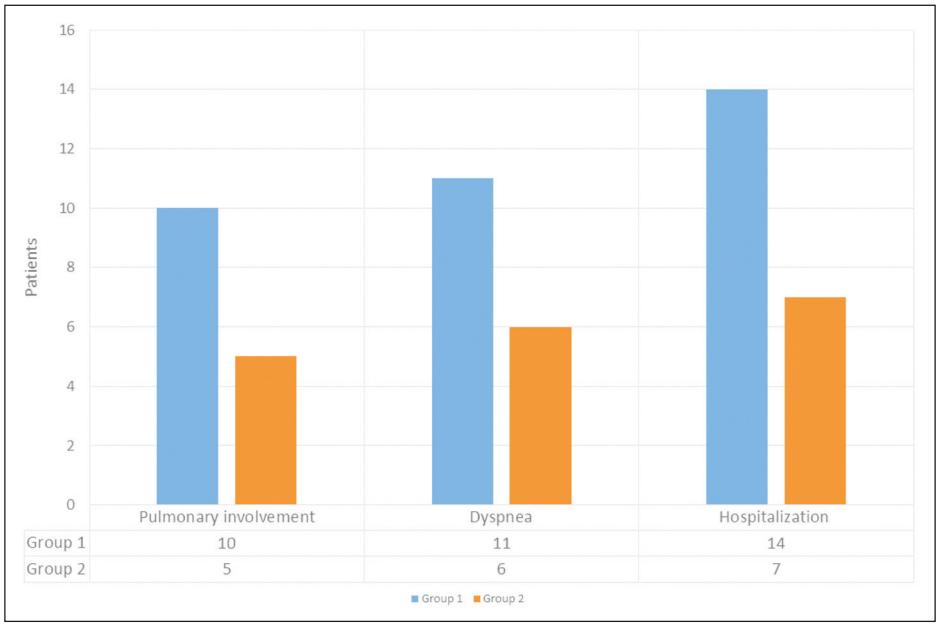

FIGURE 1: The comparison of pulmonary involvement, dyspnea, and hospitalization between groups.

not determined between the groups regarding intravesical BCG treatment and the risk of contracting COVID-19. Similarly, there was no difference in fever and cough symptoms between those who received BCG treatment and those who did not. However, COVID-19-associated symptoms such as dyspnea, lung involvement, and hospitalization requirement were less in the group that received intravesical BCG treatment. Mortality in both groups was seen in patients over 75 years and with other diseases, but without a statistically significant difference. Thus, therapies such as BCG that stimulate systemic immunity can be used to treat COVID-19 in the future.

The heterologous benefits of the BCG vaccine against non-tuberculosis infections are well known. Moreover, its protection against viruses such as the RSV, influenza A virus, and HSV Type 2 has also been reported.[10] Most notably, BCG vaccination of neonates might decrease overall childhood mortality. This includes mortality unrelated to tuberculosis, mainly driven by a decrease in sepsis and respiratory infections in childhood.[7,8] In a prospective study conducted in Japan, the BCG vaccine reportedly protected the elderly from pneumonia.[18] In another interesting study by Gofrit et al., in patients over 65 years of age, the incidence of Alzheimer's disease was four times less in those who received intravesi-

cal BCG treatment for bladder cancer than those who did not receive BCG.[19] The main reason was that BCG affected cellular and molecular mechanisms against viral infections.[9]

The ACE-2 receptors are one of the entry points of the COVID-19 virus into human cells.[20] Reduction in ACE-2 receptors is considered beneficial for host defense against COVID-19. Previous animal studies have shown that BCG-induced inflammation increases ACE-like activity. Consequently, it suppresses the induction of the inflammatory response in both lungs and spleen.[16] In another randomized-controlled study, a group of patients was vaccinated with BCG before vaccinating against yellow fever viremia. Participants who had the earlier BCG vaccine shot showed reduced yellow fever viremia. Moreover, a reduced yellow fever disease-initiated "cytokine storm" was observed in the BCG vaccine group.[21] According to these authors, BCG stimulates the T helper-1 (Th1) response. However, yellow fever (and most likely COVID-19) stimulates the Th2 response. But Th1 stimulation is a natural way of reducing the Th2 response.[22] This is particularly interesting as decreased cytokine levels cause disease severity without affecting the longer-term humoral antibody. The BCG vaccine has several heterogenous benefits. The association between the BCG vaccine and COVID-19 is controversial. Epidemic studies were conducted in countries with and without the BCG vaccine in the national vaccination program. A lower incidence of COVID-19 and related mortality were observed in the vaccinated group despite limitations such as heterogeneity of the groups and differences in diagnosis and treatment among countries.[23] Therefore, ongoing trials are investigating BCG vaccination to mitigate COVID-19 infection/morbidity.[22] In the present study, intravesical BCG application did not affect the incidence of COVID-19. Nevertheless, BCG application reduced hospitalization rates and lung involvement, although the mechanism of action could not be fully explained.

BCG has been used in NMIBC for a long time. Yet, its mechanism of action in urology is not completely clear. The internalization of BCG secretes cytokines and chemokines in the urinary and bladder tissue after cancer cells bind to fibronectin in the bladder wall. Thus, BCG upregulates the immune system.[24]

The local effects of intravesical BCG are frequently discussed. However, it also displays systemic immunological effects. In a preclinical study examining the systemic effect of intravesical BCG, strains were observed in culture in serum precipitin after injecting BCG into the canine bladder. This condition supports systemic absorption.[25] In another study, cytokines, and chemokines peaked in the urothelium within 2-8 h of beginning the BCG treatment, stimulating the immune system. Bladder cancer survival rates were higher in cases whose purified protein derivative test was positive; this was one of the systemic response indicators after intravesical BCG treatment.[14] Another study showed that intravesical BCG caused a significant systemic effect in the form of the humoral response. The immunoglobulin G level increased against tuberculin and mycobacterial heat shock protein. This antibody response gradually increased up to three months after completing the 6-week BCG course.[26] Moreover, intravesical BCG is associated with a reduced risk of developing Alzheimer's disease or other dementia among NMIBC patients.[27] The above-mentioned studies provide sufficient evidence supporting the systemic immunological effect of BCG.

The present study aimed to evaluate the literature reports. Hence, patients who received the BCG induction and maintenance courses one year before the COVID-19 outbreak in our country and those who received the BCG treatment after COVID-19 were evaluated. The efficacy of the intravesical BCG treatment, both local and systemic, was investigated.[16,26] The potential benefits and risks of BCG application during the COVID-19 pandemic should be responsibly evaluated by every urologist. While making any decision, many factors are considered because of limited data (such as patient and hospital-related factors). Rather than evidence-based guidelines, other factors are evaluated for the eligible patients.[28] However, in high-risk NMIBC patients, maintenance BCG reduces the recurrence and progression rates by approximately 15% and 4%, respectively. Intravesical BCG therapy courses continuing for more than a year can be safely terminated

for high-risk NMIBC patients.[24] The hospitals were not pandemic hospitals, and the application of the BCG procedure was rapid. Hence, patients evaluated in the present study were more compatible with the treatment regime.

The present study observed that intravesical BCG treatment did not affect the rate of COVID-19 detection in patients. However, it reduced lung involvement and hospitalization with its possible systemic effect.[16,26] It is challenging to explain the etiopathogenesis of these observations. BCG is known to stimulate humoral immunity. Moreover, easier activation of the cells responsible for immunity, especially monocytes, and the increased expression of higher cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor, may be effective. Furthermore, the strengthening of the antiviral response due to BCG may be one of the possible reasons. The retrospective study by Fedeli et al. observed no difference between the patients who received intravesical BCG treatment until five years ago and the population in terms of COVID-19 capture, hospitalization, and COVID-19-related deaths. However, their study provided no information about the BCG doses of the patients. They compared the patients who were given BCG instillation for up to five years before the pandemic outbreak.[29] This difference may be attributed to evaluating patients who were currently taking BCG treatment and who received at least six doses of BCG. The T cells responsible for active immunity are activated during BCG treatment.[14] It was difficult to determine the amount of BCG in the bladder required to stimulate a systemic effect. Yet, maintenance doses stimulate immunity constantly. Another study that supports this situation shows that older people may not have an adequate monocyte pool several years after BCG vaccination as a child.[10] Again, children vaccinated with BCG are less susceptible to infection with SARS-CoV-2 and even those infected are asymptomatic. Thus, the humoral immunity effect is less operative in patients with recent BCG contact. The same may be the case with BCG application to the bladder. BCG vaccination in healthy individuals is beneficial by stimulating immunity in the early period. It inhibits viral replication and decreases viral loads. Subsequently, it causes less inflammation and symptoms, according to several clinical studies.[10]

In contrast, Gallegos et al. observed a lower fatality rate due to COVID-19 in elderly patients receiving BCG treatment compared to the national records, albeit the number of patients was small.[30] The results of the current study were similar to those by Gallegos et al. BCG treatment positively affected the course of the disease against COVID-19. Administration of BCG to the bladder may also show similar effects by stimulating molecular and humoral immunity.[30]

In addition, despite vaccination programs and social measures, the COVID-19 pandemic would spread. Mutations of the virus, inability to predict the recovery period of infected patients, re-infection of the virus, or residual infections increase the spread.[4] BCG may be an excellent alternative to reduce morbidity and mortality, especially in elderly patients with weak immunity and in cases where the vaccination procedure will be delayed. Therefore, the outcomes of the Phase 3 studies are important.

The present study compared homogeneous groups as far as possible. No statistically significant differences were observed in the demographic findings of the patients, such as age, gender, height, and weight between the groups. Moreover, as the clinics participating in the present study were important tertiary centers of the region, intravesical BCG applications during the pandemic period could be continued. And this helped generate the population for the present study. Although patients refrain from hospital visits during this period, continuous, uninterrupted intravesical BCG treatment will contribute to the oncological results and reduce the morbidity of COVID-19 disease.

The current study had significant limitations. The first was the difference in the demographic and genetic factors of the population. The second was the patient-specific measures (such as quarantine and social distancing). The third difference was in the study design during the diagnosis and follow-up of COVID-19 cases since the present study was retrospective. The fourth difference lay in difficulty in predicting individual differences in responses of each

patient to the BCG doses. Four standard BCG doses were administered to all patients, yet each patient responded differently.

CONCLUSION

Intravesical BCG treatment applied as part of bladder tumor treatment positively reduces the morbidity caused by COVID-19. Therefore, the installation schemes should not be delayed due to the pandemic. The action mechanisms are not completely understood. Yet, the current findings are sufficient to contribute to vaccine studies.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** Mehmet Serkan Özkent, Yunus Emre Göger; **Design:** Mehmet Serkan Özkent, Yunus Emre Göger; **Control/Supervision:** Yunus Emre Göger, Mehmet Artaç; **Data Collection and/or Processing:** Mehmet Serkan Özkent, Nurullah Altınkaya; **Analysis and/or Interpretation:** Mehmet Serkan Özkent, Yunus Emre Göger, Nurullah Altınkaya, Mehmet Artaç; **Literature Review:** Mehmet Serkan Özkent, Yunus Emre Göger, Nurullah Altınkaya, Mehmet Artaç; **Writing the Article:** Mehmet Serkan Özkent, Yunus Emre Göger, Nurullah Altınkaya, Mehmet Artaç; **Critical Review:** Mehmet Serkan Özkent, Yunus Emre Göger, Nurullah Altınkaya, Mehmet Artaç; **References and Fundings:** Mehmet Serkan Özkent, Nurullah Altınkaya; **Materials:** Nurullah Altınkaya.*

REFERENCES

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533-534. Erratum in: Lancet Infect Dis. 2020;20(9):e215. [Crossref] [PubMed]
2. Lloyd-Sherlock P, Ebrahim S, Geffen L, McKee M. Bearing the brunt of covid-19: older people in low and middle income countries. BMJ. 2020;368:m1052. [Crossref] [PubMed]
3. Mogaji E. Financial vulnerability during a pandemic: insights for coronavirus disease (COVID-19). Research Agenda Working Papers. 2020:57-63. [Crossref]
4. Gilbert M, Pullano G, Pinotti F, et al. Preparedness and vulnerability of African countries against importations of COVID-19: a modelling study. Lancet. 2020;395(10227):871-877. [Crossref] [PubMed] [PMC]
5. He F, Deng Y, Li W. Coronavirus disease 2019: what we know? J Med Virol. 2020;92(7):719-725. [Crossref] [PubMed] [PMC]
6. Colditz GA, Berkey CS, Mosteller F, et al. The efficacy of bacillus Calmette-Guérin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. Pediatrics. 1995;96(1 Pt 1):29-35. [Crossref] [PubMed]
7. Higgins JP, Soares-Weiser K, López-López JA, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. BMJ. 2016;355:i5170. Erratum in: BMJ. 2017;356:j1241. [Crossref] [PubMed] [PMC]
8. Hollm-Delgado MG, Stuart EA, Black RE. Acute lower respiratory infection among Bacille Calmette-Guérin (BCG)-vaccinated children. Pediatrics. 2014;133(1):e73-81. [Crossref] [PubMed]
9. Moorlag SJCFM, Arts RJW, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. Clin Microbiol Infect. 2019;25(12):1473-1478. [Crossref] [PubMed]
10. O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? Nat Rev Immunol. 2020;20(6):335-337. [Crossref] [PubMed] [PMC]
11. Mantovani A, Netea MG. Trained innate immunity, epigenetics, and Covid-19. N Engl J Med. 2020;383(11):1078-1080. [Crossref] [PubMed]
12. Babjuk M, Böhle A, Burger M, et al. EAU Guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol. 2017;71(3):447-461. [Crossref] [PubMed]
13. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol. 2016;196(4):1021-1029. [Crossref] [PubMed]
14. Crispen PL, Kusmartsev S. Mechanisms of immune evasion in bladder cancer. Cancer Immunol Immunother. 2020;69(1):3-14. [Crossref] [PubMed] [PMC]
15. Fuge O, Vasdev N, Allchorne P, Green JS. Immunotherapy for bladder cancer. Res Rep Urol. 2015;7:65-79. [Crossref] [PubMed] [PMC]
16. Desouky E. BCG versus COVID-19: impact on urology. World J Urol. 2021;39(3):823-827. [Crossref] [PubMed] [PMC]
17. Redelman-Sidi G. Could BCG be used to protect against COVID-19? Nat Rev Urol. 2020;17(6):316-317. [Crossref] [PubMed] [PMC]
18. Ohrui T, Nakayama K, Fukushima T, Chiba H, Sasaki H. [Prevention of elderly pneumonia by pneumococcal, influenza and BCG vaccinations]. Nihon Ronen Igakkai Zasshi. 2005;42(1):34-36. Japanese. [Crossref] [PubMed]
19. Gofrit ON, Klein BY, Cohen IR, Ben-Hur T, Greenblatt CL, Bercovier H. Bacillus Calmette-Guérin (BCG) therapy lowers the incidence of Alzheimer's disease in bladder cancer patients. PLoS One. 2019;14(11):e0224433. [Crossref] [PubMed] [PMC]

20. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;8(4):e21. Erratum in: Lancet Respir Med. 2020;8(6):e54. [Crossref] [PubMed] [PMC]

21. Arts RJW, Moorlag SJCFM, Novakovic B, et al. BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. Cell Host Microbe. 2018;23(1):89-100.e5. [Crossref] [PubMed]

22. Brooks NA, Narayan V, Hegarty PK, Zafirakis H, Han XY, Kamat AM. The role of the urologist, BCG vaccine administration, and SARS-CoV-2: an overview. BJUI Compass. 2020;1(3):87-92. [Crossref] [PubMed] [PMC]

23. Hegarty PK, Kamat A, Zafirakis H, Dinardo A. BCG vaccination may be protective against Covid-19. 2020. [Crossref]

24. Böhle A, Brandau S. Immune mechanisms in bacillus Calmette-Guerin immunotherapy for superficial bladder cancer. J Urol. 2003;170(3):964-969. [Crossref] [PubMed]

25. Schellhammer PF, Kaplan MH, Pinsky CM, Whitmore WF Jr. Study of local and systemic effects of intravesical BCG. Urology. 1975;6(5):562-567. [Crossref] [PubMed]

26. Zlotta AR, Drowart A, Huygen K, et al. Humoral response against heat shock proteins and other mycobacterial antigens after intravesical treatment with bacille Calmette-Guérin (BCG) in patients with superficial bladder cancer. Clin Exp Immunol. 1997;109(1):157-165. [Crossref] [PubMed] [PMC]

27. Kim JI, Zhu D, Barry E, Kovac E, Aboumohamed A, Agalliu I, Sankin A. Intravesical bacillus calmette-guérin treatment is inversely associated with the risk of developing Alzheimer disease or other dementia among patients with non-muscle-invasive bladder cancer. Clin Genitourin Cancer. 2021;19(6):e409-e416. [Crossref] [PubMed]

28. Lenfant L, Seisen T, Loriot Y, Rouprêt M. Adjustments in the use of intravesical instillations of bacillus calmette-guérin for high-risk non-muscle-invasive bladder cancer during the COVID-19 pandemic. Eur Urol. 2020;78(1):1-3. [Crossref] [PubMed] [PMC]

29. Fedeli U, Porreca A, Colicchia M, Schievano E, Artibani W, Biasio LR, Palù G. Intravescical instillation of Calmette-Guérin bacillus and COVID-19 risk. Hum Vaccin Immunother. 2021;17(2):416-417. [Crossref] [PubMed] [PMC]

30. Gallegos H, Rojas PA, Sepúlveda F, Zú-iga Á, San Francisco IF. Protective role of intravesical BCG in COVID-19 severity. BMC Urol. 2021;21(1):50. [Crossref] [PubMed] [PMC]