

## ORIGINAL PAPER

# Patterns of treatment of high-risk BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) patients among Arab urologists

Mohamad Moussa<sup>1, 2\*</sup>, Mohamad Abou Chakra<sup>1, 3\*</sup>, Neal D. Shore<sup>4</sup>, Athanasios Papatsoris<sup>1, 5</sup>, Yasser Farahat<sup>6, 7</sup>, Michael A. O'Donnell<sup>3</sup>

<sup>1</sup> Department of Urology, Lebanese University, Beirut, Lebanon;

<sup>2</sup> President of the Arab Association of Urology (AAU);

<sup>3</sup> Department of Urology, University of Iowa, Iowa City, Iowa, USA;

<sup>4</sup> Carolina Urologic Research Center, Myrtle Beach, South Carolina, USA;

<sup>5</sup> 2<sup>nd</sup> Department of Urology, School of Medicine, Sismanoglio Hospital, National and Kapodistrian University of Athens, Athens;

<sup>6</sup> Urology Department, Sheikh Khalifa General Hospital, Umm Al Quwain, United Arab Emirates;

<sup>7</sup> Secretary General of the Arab Association of Urology (AAU);

\* Both authors contributed equally to this work.

## Summary

**Purpose:** To understand the treatment plans suggested for BCG-unresponsive non-muscle invasive disease (NMIBC) patients in the Arab countries and therapeutic decisions applied for BCG-naïve patients during BCG shortage time.

**Methods:** A 10-minute online survey was distributed through the Arab Association of Urology (AAU) office to urologists in the Arab countries who treat patients with NMIBC.

**Results:** One hundred six urologists responded to the survey. The majority of urologists had treated, in the past 6 months, > 10 patients with NMIBC who were considered BCG-unresponsive (55% of respondents). Radical cystectomy (RC) was the most popular treatment option (recommended by 50%) for these patients. This was followed by intravesical chemotherapy (30%), repeat BCG therapy (12%), resection with ongoing surveillance (8%). Clinical trials and intravenous checkpoint inhibitors were never selected. The most preferred intravesical chemotherapy was by ranking: 60% gemcitabine, 19% mitomycin C, 8% docetaxel, 8% gemcitabine/docetaxel, 4% sequential gemcitabine/mitomycin C, and 1% valrubicin. The use of intravesical chemotherapy appears limited by Arab urologists due to concerns regarding clinical efficacy (fear of progression) and the lack of clear recommendations by urology societies. Given the BCG shortage, which may vary per Arab country, Arab urologists have adjusted by prioritizing BCG for T1 and carcinoma in situ (CIS) patients over Ta, adapting intravesical chemotherapy, and reducing the dose/strength of BCG administered. Most physicians report an eagerness to utilize novel therapies to address the BCG deficit, especially to try intravesical chemotherapy.

**Conclusions:** Even though Arab urologists are in the majority of cases selecting RC for BCG-unresponsive cases, one-third of them are most recently initiating intravesical chemotherapy as an alternative option. To further assist Arab urologists in the appropriate selection of BCG unresponsive high risk NMIBC patient treatments, enhanced education and pathway protocols are needed.

**KEY WORDS:** Non-muscle invasive bladder cancer; BCG unresponsive; Practice pattern; Arab urologists; BCG shortage.

Submitted 30 December 2023; Accepted 17 January 2024

## INTRODUCTION

High-Risk (HR) non-muscle-invasive bladder cancer (NMIBC) is an aggressive disease with significant risks of both recurrence and progression. Intravesical *Bacillus Calmette-Guérin* (BCG) has been the standard of therapy for NMIBC for decades (1). Unfortunately, despite front-line BCG therapy, progression to muscle-invasive cancer can occur in up to 20% of cases, especially during the first 2 years of the disease (2). Thus, a proper definition of the BCG disease state is crucial for the appropriate management of NMIBC. This includes BCG-naïve patients and BCG-unresponsive patients. Most recently, a new category has emerged between the two groups called BCG exposed patients (aka, less than adequate) which includes patients in whom BCG has failed but does not include the guidelines mandated criteria necessary for defining BCG-unresponsive (3, 4). The current standard of care for BCG-unresponsive cases does not include repeat BCG therapy or rechallenge with BCG (5).

The management of NMIBC cases has been challenged by BCG shortages that started in 2012. This may increase the number of patients in the BCG-exposed group and, subsequently, BCG-failed cases (6). Urological societies have recommended radical cystectomy (RC) as the best choice for patients in whom BCG has failed (4, 7). However, many patients are assuredly reluctant to undergoing this major life altering operation. Thus, numerous intravesical chemotherapy regimens such as gemcitabine (Gem), mitomycin C (MMC) valrubicin, and a combination of gemcitabine and docetaxel (Gem/Doce) and gemcitabine and mitomycin (Gem/MMC) have emerged despite a lack of formal regulatory approvals. These therapies may offer promising results with less toxicity than BCG for some patients (8). Interestingly, only three treatment options have been approved by the US Food and Drug Administration (FDA) for BCG unresponsive carcinoma in situ (CIS) tumors: intravesical valrubicin (1998), systematic pembrolizumab (2020), and Nadofaragene firadenovec, a non-replicating adenovirus that produces human interferon alpha-2b

(2022) (9). The application of these therapies is limited by their narrow indication for only CIS-containing tumors, their cost, and their limited worldwide availability. Our survey suggests a paucity of knowledge about the treatment plans utilized for BCG-unresponsive NMIBC patients in Arab countries. The purpose of this survey was to learn more about the therapies and options provided to NMIBC patients who fail adequate BCG therapy. Additional goals included determining which intravesical agents are currently preferred as second-line therapy while understanding the obstacles to offering and implementing new therapeutic alternatives. In addition, we aimed to assess the practice pattern of urologists during the BCG shortage. The results of the survey will be utilized to establish best practices for the better management of BCG-unresponsive NMIBC cases in the Arab Region.

## MATERIALS AND METHODS

### Survey method

Arab urologists received by email a web-based survey with a 10-minute time expectation to complete. This survey was sent through the *Arab Association of Urology* office to urologists recorded in their database. More than ten thousand urologists in the Arab world are members of the AAU. Data were collected from 22 Arab countries between October 17 and November 17, 2023 (Table 1). Participation in the survey was completely voluntary and anonymous for all respondents. No patient records have been collected. Responses were kept confidential at all stages of data analysis.

**Table 1.**

*Number of respondents according to country of practice in the Arab region.*

Country	Number of respondents
Algeria	5
Bahrain	14
Comoros	0
Djibouti	0
Egypt	12
Iraq	10
Jordan	4
Kuwait	5
Lebanon	16
Libya	0
Mauritania	0
Morocco	4
Oman	9
Palestine	0
Qatar	6
Saudi Arabia	5
Somalia	0
Sudan	0
Syria	0
Tunisia	4
United Arab Emirates	7
Yemen	5

### Questionnaire design

The survey included questions on eligibility, treatment preferences, and regimens used for NMIBC patients who are BCG unresponsive, as well as the views of urologists regarding the use of intravesical chemotherapy in those patients and the challenges are encountered. Choosing the next course of treatment and managing BCG-unresponsive patients other than by radical cystectomy was queried. Additional inquiries were made concerning BCG shortages and the course of action taken to manage BCG-naïve cases during shortages.

### Statistical analysis

Descriptive statistics were used to analyze the data for all combined countries. To adequately portray the data, frequencies and percentages were employed for categorical variables. There was no missing data because respondents had to complete each question before moving on to the next, and a 'don't know' answer was not allowed.

## RESULTS

### Survey respondent demographics and general practice outlines

A survey was sent to the AAU members (more than thousand members), and one hundred and six urologists responded to the survey. Among the respondents, 46% were in academic-based practice, 19% in community-based practice, and the other 35% were in a mix of academic and community-based practice. 46% of urologists were subspecialized in urologic oncology and 8% in endourology, while the other 46% were general urologists. The majority of urologists had experience managing NMIBC for 10 to 20 years (25%) and > 20 years (49%). Concerning guidelines followed in the management of NMIBC, 31% chose *American Urological Association* (AUA) guidelines, 36% chose *European Association of Urology* (EAU) guidelines, 28% chose *National Comprehensive Cancer Network* (NCCN) guidelines, and 5% chose other guidelines (*Society of Urologic Oncology* (SUO) and local guidelines).

### Management strategy for high-risk BCG-unresponsive NMIBC

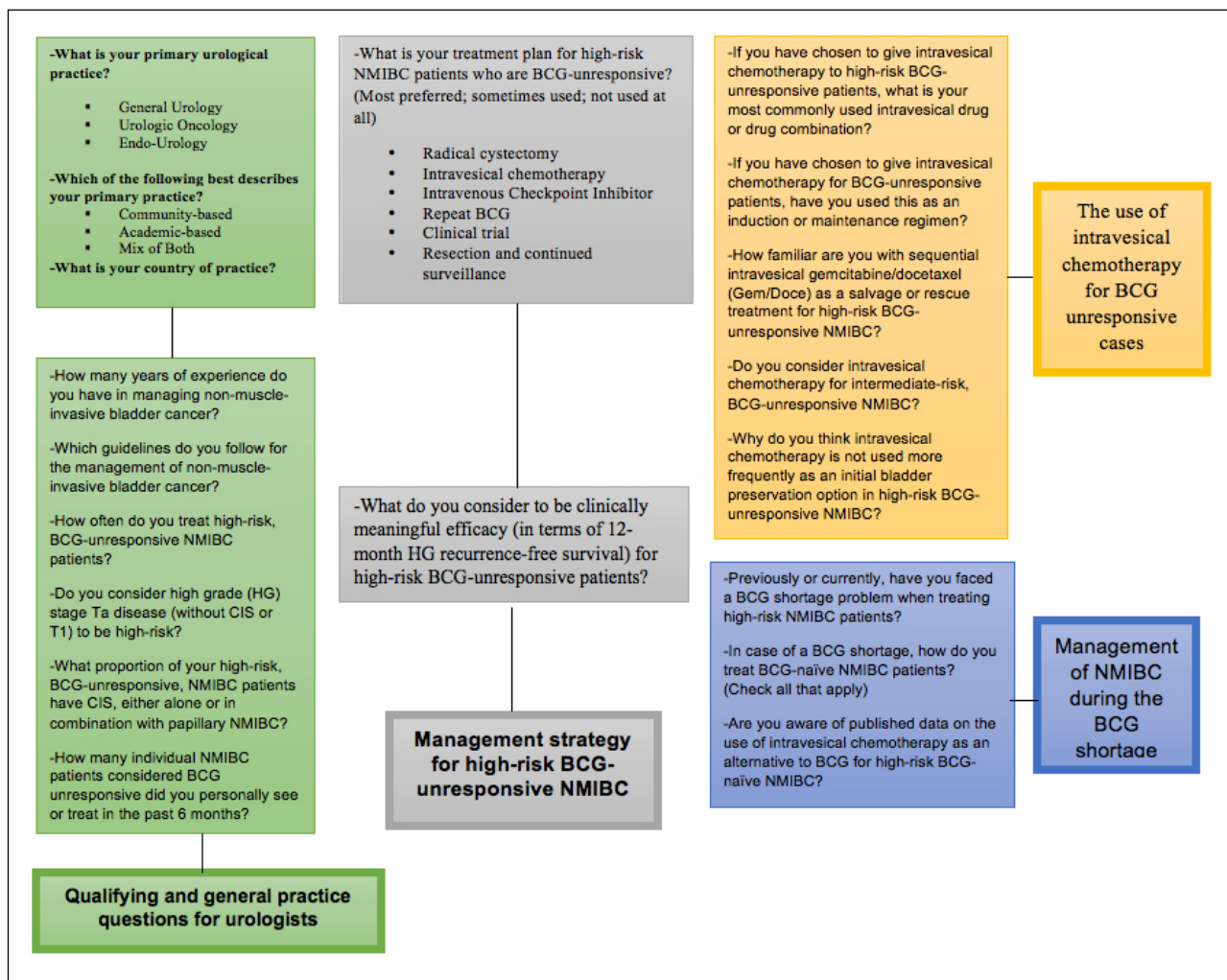
The majority of urologists had treated > 10 patients in the past 6 months with NMIBC who were considered BCG unresponsive (55% of respondents), while 45% reported treating < 10 of these patients in the last 6 months. When asked about the number of *high-risk* (HR) BCG unresponsive patients treated per month, 66% of urologists reported treating more than 5 patients per month.

In terms of the proportion of CIS tumors in HR disease, 58% reported treating a proportion > 20%. 22% of urologists consider *high-grade* (HG) Ta disease (without CIS or T1) as an HR tumor; 66% of respondents only consider this type of tumor as HR if the tumor is large (> 3 cm), multifocal, or multi-recurrent (> 1 recurrence per year); and 12% do not consider this type of disease as HR regardless of additional clinical factors. A detailed response on tumor characteristics is summarized in Figures 2a, b.

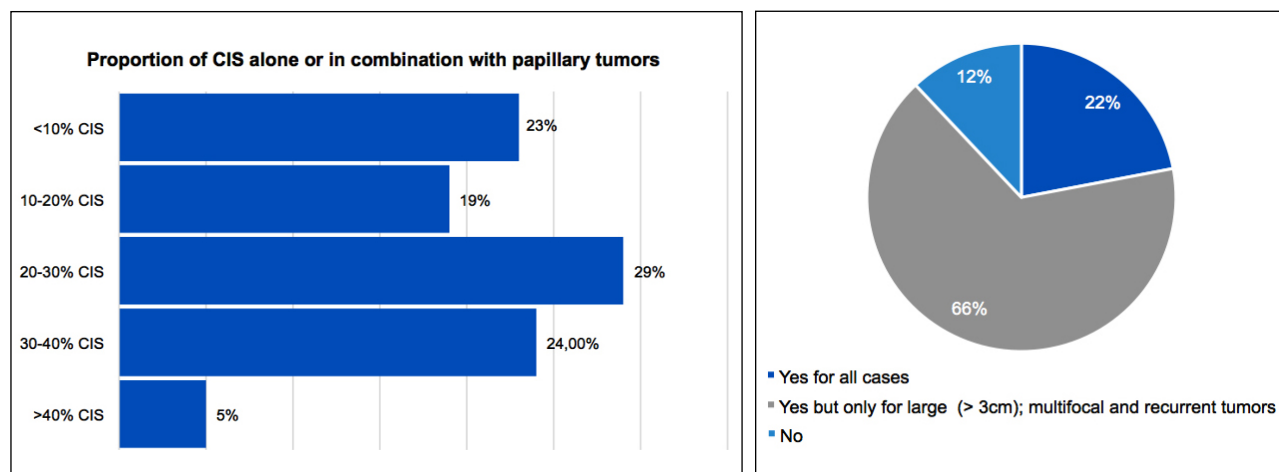
When questioned on the management strategy for high-

**Figure 1.**

Survey-relevant questions delivered to urologists.



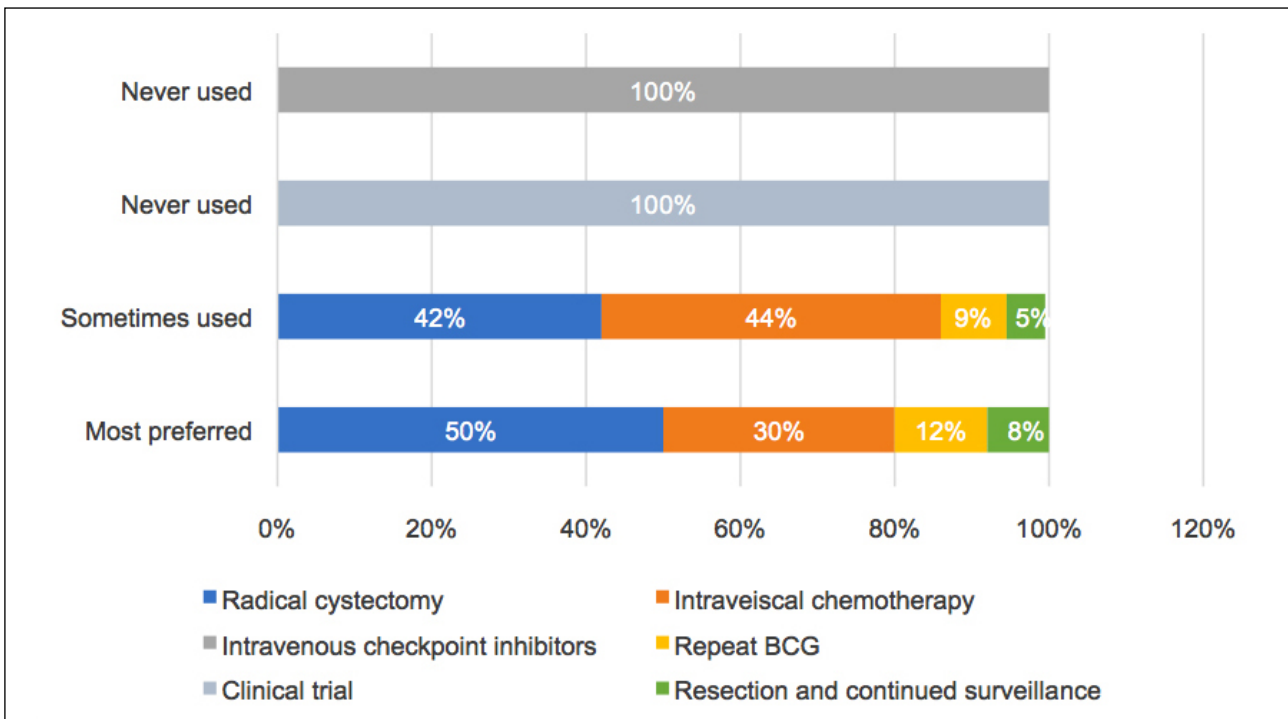
CIS: carcinoma in situ; BCG: bacille Calmette-Guerin; NMIBC: non-muscle invasive bladder cancer.

**Figure 2.****A.** Proportion of CIS tumors found in high-risk, BCG-unresponsive, NMIBC patients.**B.** Percentage of urologists considering HG-stage Ta disease (without CIS or T1) to be high-risk tumors.

CIS: carcinoma in situ.

**Figure 3.**

Management strategy for high-risk NMIBC patients who are BCG-unresponsive.



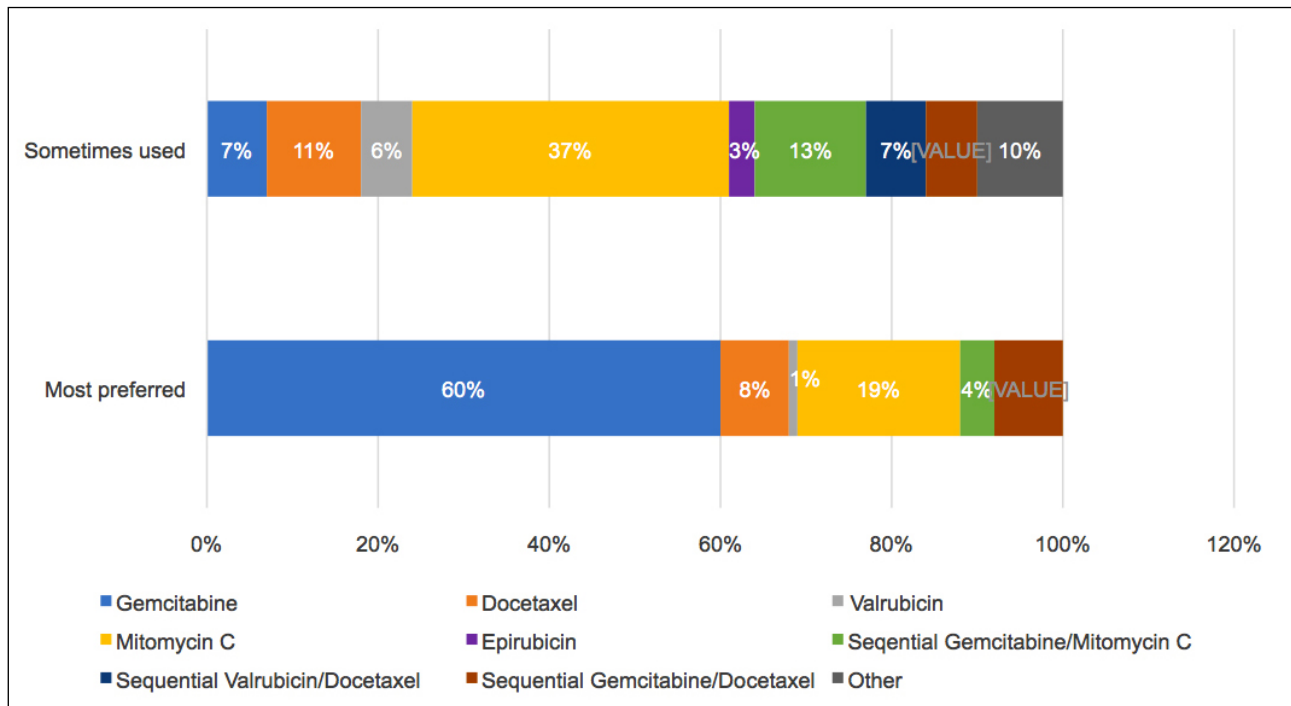
NMIBC: non-muscle-invasive bladder cancer

risk NMIBC patients who are BCG-unresponsive, most preferred RC (50%) followed by intravesical chemotherapy (30%), repeat BCG therapy (12%), and resection with

continued surveillance (8%). Intravenous checkpoint inhibitors and clinical trials were never selected. The treatment strategy used by urologists is listed in Figure 3.

**Figure 4.**

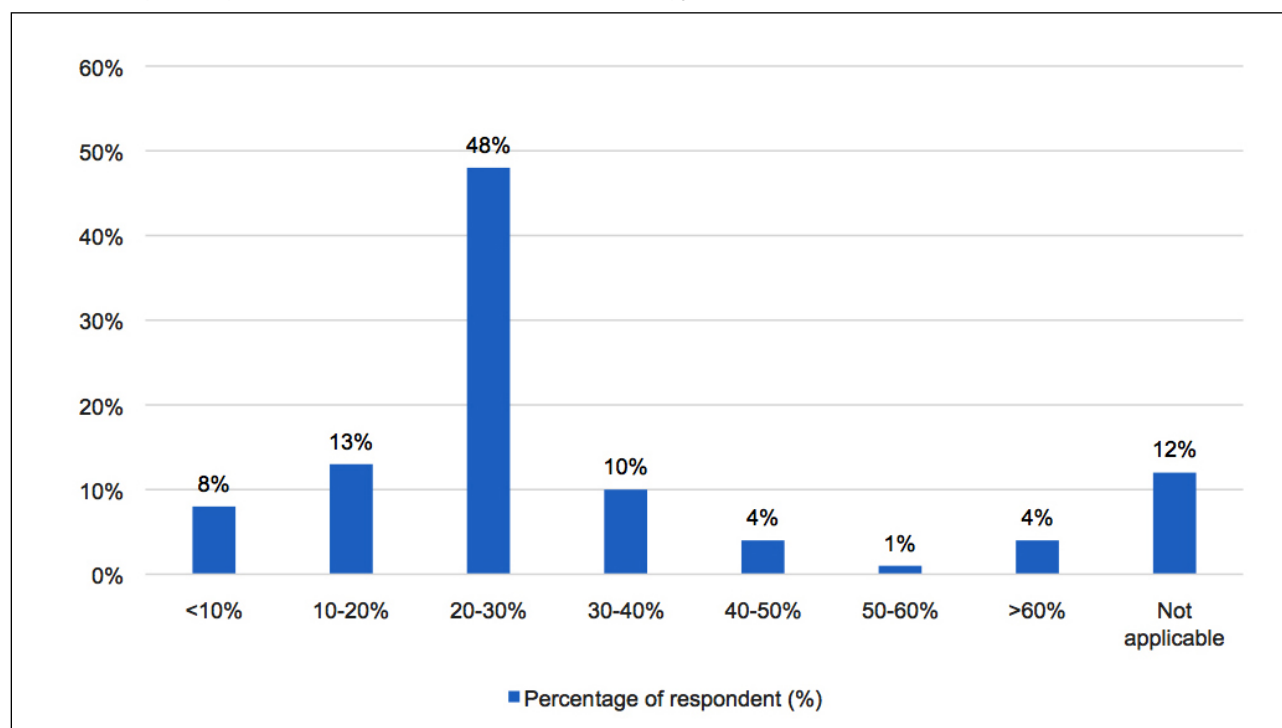
The most commonly used intravesical drug or drug combination for high-risk BCG-unresponsive patients.





**Figure 5.**

Clinically meaningful efficacy (in terms of 12-month high-grade recurrence-free survival) for BCG-unresponsive patients treated with intravesical chemotherapy.



When RC was chosen, 66% of urologists personally performed the cystectomy, while 34% referred patients to another center for cystectomy.

#### **The use of intravesical chemotherapy for BCG unresponsive cases**

With regard to the most commonly used intravesical drug or combination of drugs, 60% reported gemcitabine, 19% MMC, 8% docetaxel, 8% Gem/Doce, 4% sequential Gem/MMC, and 1% valrubicin. The sometimes-used regimens varied with a rank order of 37% MMC, 13% sequential Gem/MMC, 11% docetaxel, 7% gemcitabine, 7% Valrubicin/Docetaxel, 6% Gem/Doce, 6% valrubicin, 3% epirubicin, and 10% other agents. The detailed drugs used for intravesical chemotherapy are summarized in Figure 4. 60% of urologists used intravesical chemotherapy for induction and maintenance, while the other 40% used it for induction only.

Urologists were also specifically asked what level of clinical response would be a sufficient at 1 year to be clinically meaningful for high-risk BCG-unresponsive patients. Almost 50% of urologists define a 12-month HG RFS of at least 20-30% (Figure 5).

Reporting on the use intravesical chemotherapy for intermediate-risk disease among BCG-failures, 21% of urologists mentioned that they would use further intravesical chemotherapy as a preferred therapy, 27% would use it as a second line treatment, and 52% would never use it in such a situation.

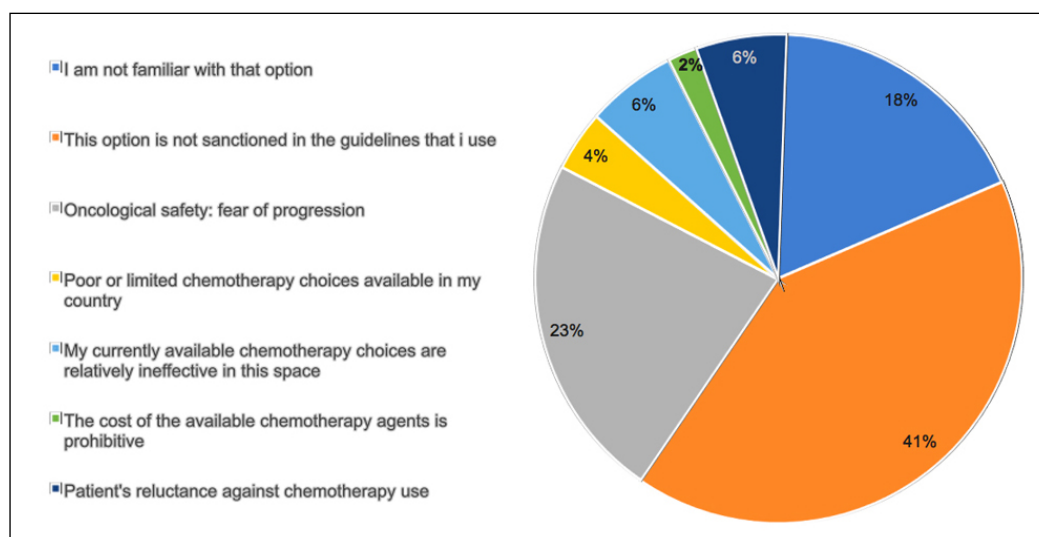
A separate question inquired about the familiarity of urologists with sequential intravesical Gem/Doce as salvage therapy for BCG-unresponsive HR-NMIBC patients. Only

14% of urologists currently use this therapy but are still evaluating its efficacy; 33% were familiar with this therapy but considered it outside their current practice; and the majority (53% of respondents) were not familiar enough with treatment to consider using it in their daily practice.

The predominant reasons for not frequently using intravesical chemotherapy as a bladder preservation option in HR BCG-unresponsive NMIBC were investigated. 18% of urologists were not familiar with many of the intravesical chemotherapy regimens; 41% stated that bladder sparing options were not sanctioned in the guidelines that they use; while 23% were reluctant due to concern for progression of tumor after usage of those drugs. Other reasons cited included patients' refusal of chemotherapy use, limited availability, or cost of treatment (18%) (Figure 6).

#### **Management of NMIBC during the BCG shortage**

In a question inquiring about the current BCG shortage issue faced by urologists when treating HR NMIBC, 68% of respondents confirmed the ongoing shortage, 21% mentioned that they had some shortage problems but not in the past 6 months, and 11% had no shortage at all (Table 2). To treat BCG-naïve patients in cases of BCG shortage, 45% of urologists prioritize BCG for T1 and CIS patients over Ta, 16% switch to intravesical chemotherapy, 15% use dose reduction of BCG (1/2 to 1/3 dose), 14% prioritize BCG for the higher-risk groups, 5% shorten the duration of maintenance therapy, 3% perform radical cystectomy, and 2% just wait to get BCG (Figure 7). Additional questions were asked enquiring about the published data on the use of intravesical chemotherapy as an alternative to BCG for HR BCG-naïve NMIBC. Only



**Figure 6.**  
The most common reasons for not using intravesical chemotherapy as an initial bladder preservation option in high-risk BCG-unresponsive NMIBC.

**Table 2.**

BCG supplements according to country of practice in the Arab region.

Country	Number of respondents	Ongoing shortage	Some shortage but not in the past 6 months	No shortage at all
Algeria	5	5	-	-
Bahrain	14	8	4	2
Comoros	0	-	-	-
Djibouti	0	-	-	-
Egypt	12	5	4	3
Iraq	10	7	3	-
Jordan	4	2	1	1
Kuwait	5	1	3	1
Lebanon	16	15	1	-
Libya	0	-	-	-
Mauritania	0	-	-	-
Morocco	4	2	2	-
Oman	9	7	-	2
Palestine	0	-	-	-
Qatar	6	3	-	3
Saudi Arabia	5	2	3	-
Somalia	0	-	-	-
Sudan	0	-	-	-
Syria	0	-	-	-
Tunisia	4	4	-	-
United Arab Emirates	7	6	1	-
Yemen	5	5	-	-
		72 (68%)	22 (21%)	12 (11%)

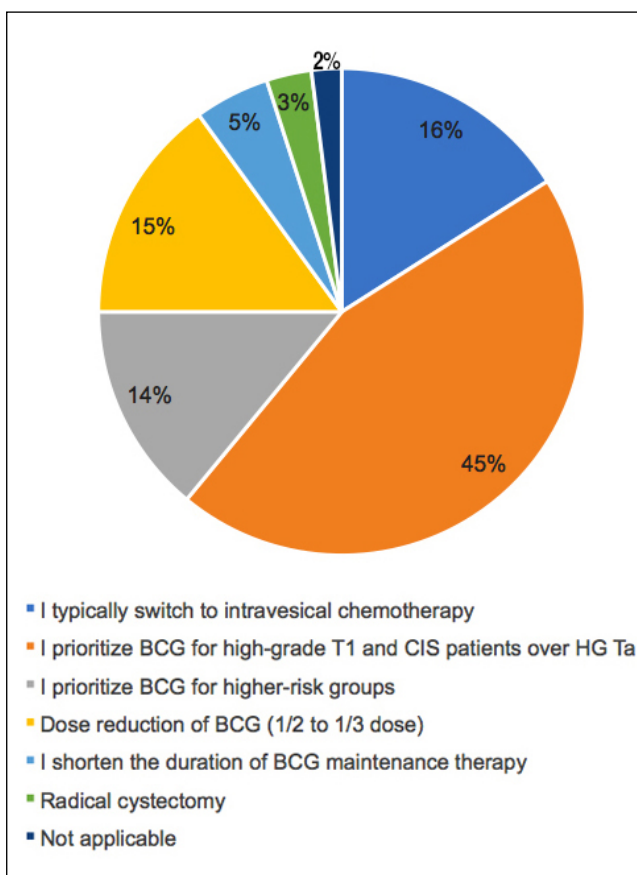
21% were not aware of the data published on the topic, and 27% had limited familiarity with the data. 34% of urologists would use intravesical chemotherapy if BCG were unavailable, and 18% think the current published data is sufficient to consider certain chemotherapy regimens (Gem/Doce) as a first-line alternative to BCG.

## DISCUSSION

The management of BCG-unresponsive disease is challenging. While new therapies have emerged and addi-

**Figure 7.**

Frequency of options used by urologists to treat BCG-naïve NMIBC patients during the BCG shortage.



tional novel therapies may soon receive approvals, intravesical chemotherapy remains a real-world, practical and efficacious alternative. Several points are notable from this survey of Arab Country Urologists.

**First,** RC was chosen as the most preferred initial therapy for BCG-unresponsive cases by half of the Arab urologists. This is not consistent with previous surveys from

other regions worldwide, where RC was not selected in the majority of cases. Whereas urological societies recommend in their guidelines to do radical surgery for BCG-unresponsive cases (4, 7). In a survey in the US evaluating the practice pattern of unresponsive BCG among 259 urologists, only 24% of urologists routinely performed RC for those patients (10). Patients from the UK, France, Germany, and Canada who have received RC within the previous year, were on BCG, or had BCG unresponsiveness were invited to participate in a cross-country study by completing an online choice poll. Of the 107 participants, the majority (89%) never chose RC as their preferred form of initial treatment (11). In a US survey on therapy for NMIBC, more than 80% of urologists were reluctant to use RC right away for patients in whom BCG therapy had failed twice (12).

**Second**, intravesical chemotherapy has been used more and more in real-world practice to manage HR NMIBC cases who failed on BCG. 30% of Arab urologists mentioned this therapy as a preferred option, and up to 44% sometimes used it. While systemic checkpoint inhibitors or clinical trials have not been used, those results are quite different from those in other countries. Recently, according to US data, 55% of urologists have used intravesical chemotherapy and 14% have used intravenous checkpoint inhibitors to manage HR-BCG-unresponsive NMIBC patients. Additionally, clinical trials were proposed in less than 10% of cases from the same survey (10). In another multi-country analysis of urologic practice managing BCG unresponsive cases, data were collected in eight countries: France, Germany, Spain, Italy, the UK, the US, China, and Japan. 508 physicians were included in the study. 48.6% of physicians may use intravesical chemotherapy, and up to 64% may use intravenous checkpoint inhibitors as options for BCG failure disease (13). In additional real-world analysis of the management of BCG-unresponsive patients from three continents, initial intravesical chemotherapy was used in up to 64% of cases in China, but as low as 11% in Japan, and 12% in France. While repeat BCG therapy has been rarely used in the UK (9%), Germany (6%), and Italy (10%), it has been frequently used in China and Japan (data not shown) (14). In our survey, only 12% reported repeating BCG as their preferred option, which is in line with other countries results.

**Third**, the most commonly used intravesical chemotherapy in our survey was Gem and MMC, not unlike that reported elsewhere (10). While intravesical Gem has been widely used for BCG unresponsive cases, RFS rates at 24 months are about 40% for high-grade papillary-only cases but only about 20% for CIS-containing NMIBC (15). In contrast, sequential therapy of Gem/Doce and Gem/MMC has also been explored in this area. Gem/Doce and Gem/MMC therapy provide 24-month RFS's of over 40% in BCG failure cases, including those with CIS (8). In our survey, Gem/Doce and Gem/MMC were used by 14% and 17% of urologists, respectively. The use of these drugs is also quite different across regions worldwide. In a recent US survey, the rank order of intravesical chemotherapy used to treat HR BCG unresponsive NMIBC patients was: Gem 49%, MMC 23%, Gem/Doce 15%, Valubicin 11%, and other 2% (10). In China, the most often administered

drugs are epirubicin (37%), followed by doxorubicin (34%), and Gem (26%). In European countries like France, the UK, and Italy, intravesical MMC is the most common drug used in this setting (13).

**Fourth**, in our survey, almost 50% of urologists determined that the clinically meaningful efficacy (in terms of 12-month HG RFS) for BCG-unresponsive patients treated with intravesical chemotherapy should range from 20–30%. According to FDA guidelines, an experimental drug should have a 30% RFS rate for papillary tumors in BCG-refractory patients at 18–24 months (16). The fastest supercomputer (uniform 60,000-core cluster) was required to process a simulation model with several input parameters, such as survival probability and event timings. This was used to conduct a simulated analysis to determine which efficacy in BCG-unresponsive tumors may compete with early RC. Following model validation, it was determined that in order to provide clinically relevant efficacy, the FDA/AUA recommendation on efficacy (RFS) should be raised by at least 5% at 18–24 months (17). We note that urologists in our survey expected a lower efficacy of intravesical chemotherapy (less than 30% RFS), thus perhaps the urgent need for an alternate treatment for BCG-unresponsive disease, previous experiences with new drugs, or lack of knowledge of FDA guidelines about the effectiveness of novel therapies impacted such expectations. A proper understanding of efficacy outcomes is important in practice when interpreting emerging data from clinical trials and suggesting this treatment in shared decisions with patients.

**Fifth**, it was observed that BCG shortages are an ongoing problem in Arab countries, as 68% of urologists encountered shortages of BCG during their practice. This parallels other regions globally. Options offered to urologists to adapt to the shortage included: dose reduction of BCG, prioritizing BCG for certain tumor stages (T1 or CIS), and using second-line alternatives such as chemotherapy (18). In our survey, Arab urologists have used these strategies. Interestingly, only 21% of urologists were not aware of data published on the efficacy of intravesical chemotherapy in HR BCG-naïve NMIBC cases, and only 18% were convinced enough by the data to use the combination of Gem/Doce in this setting. Recently, a 2-year RFS of 80% was reported for Gem/Doce used as the first line treatment of HR NMIBC cases, comparable to BCG, making this combination a good choice to substitute for BCG, especially if BCG's availability is limited (19).

The Arab region consists of 22 countries that are situated in North Africa and the Middle East. The gross national income of these nations varies greatly from one another leading to significant differences in health care expenditures (20). The cost of therapy for NMIBC includes direct medical costs paid by the patient or its insurance company and indirect costs including home care costs, on-leave costs, and the loss of work productivity. Direct costs can be assessed using *gross domestic product* (GDP) per capita, based on *purchasing power parity* (PPP), according to World Bank income data (21). With Qatar's GDP per capita PPP of USD \$114,049.2 and Somalia's of USD \$1,711, there is widespread economic disparity (Table 3). The economic status of the country clearly affected the choice of therapy for BCG-unresponsive NMIBC. In high-income countries, the

Country	Number of respondents	GDP per capita PPP (current international USD)	Ongoing BCG shortage	RC	IVC	Repeat BCG	Resection and surveillance
Algeria	5	13,226.8	5	3	0	2	0
Bahrain **	14	61,248.2	8	9	5	0	0
Comoros	0	3,833.7	-	-	-	-	-
Djibouti	0	5,893.2	-	-	-	-	-
Egypt	12	15,096	5	8	4	-	-
Iraq	10	10,865.4	7	6	2	0	2
Jordan	4	11,209.9	2	2	2	0	0
Kuwait **	5	58,349.2	1	1	4	0	0
Lebanon	16	14,330.5	15	7	2	6	1
Libya	0	23,382.7	-	-	-	-	-
Mauritania	0	6,295.8	-	-	-	-	-
Morocco	4	9,547.7	2	2	-	2	-
Oman **	9	41,738.2	7	6	3	-	0
Palestine *	0	-	-	-	-	-	-
Qatar **	6	114,049.2	3	3	3	-	-
Saudi Arabia **	5	59,279.9	2	3	2	0	0
Somalia	0	1,711.0	-	-	-	-	-
Sudan	0	4,217.4	-	-	-	-	-
Syria *	0	-	-	-	-	-	-
Tunisia	4	12,483.6	4	1	1	1	1
United Arab Emirates **	7	88,489.0	6	2	4	-	1
Yemen	5	3,437.4	5	-	-	2	3
	106		72 (68%)				

\* Missing GDP per capita PPP data; \*\* High income country; PPP: Purchasing power parity; GDP: gross domestic product; IVC: intravesical chemotherapy; RC: radical cystectomy; USD: United States dollar.

**Table 3.**  
Therapy options for BCG-unresponsive disease and BCG shortage status according to country of practice in the Arab region and their GDP per capita PPP.

most preferred treatment chosen by urologists was RC or intravesical chemotherapy, whereas options like repeat BCG therapy or resection and surveillance (considered less effective) were more often chosen by urologists from low- or low-middle income countries. However, more than 20% of urologists in low-income countries are starting to use intravesical chemotherapy with only 2% of urologists reporting that the cost of drugs was the main reason for not using it (Figure 6). Making these alternatives affordable remains an important goal. Interestingly, the BCG shortage was an ongoing problem in all countries, and the prevalence of shortages was not related to income (Table 3). This is likely due to source limitations in the production of BCG. It's possible the strain of BCG used may also vary according to economic factors, but this was not assessed in our survey.

*Intra-arterial chemotherapy* (IAC) has been reported for HR-NMIBC by some groups, but in our survey, urologists did not use IAC for BCG-naïve or unresponsive disease. *Intravesical chemotherapy* (IVC) with IAC therapy prevented tumor recurrence and progression more effectively than IVC alone, with only mild to moderate side effects (22). A recent study compared the efficacy of a combination of IAC+IVC (cisplatin and epirubicin + epirubicin or pirarubicin) (n = 43) vs. BCG (n = 53) for HR-NMIBC patients. Despite having almost the same pathological stage and grade in two groups, there was no significant difference between the recurrence and progression rates. 83.1% of patients experienced adverse events linked to BCG, while 46.5% of patients experienced adverse events related to IAC (23). The combination IAC+IVC is effective in both IR and HR cases. For HR disease, the 5-year recurrence rate was reported as 56.3% vs. 26.1% in the IVC vs. IAC+IVC groups, respectively (p=0.007). For IR disease, 5 years' recurrence rate was reported as 44.4% vs.

22.2% in the IVC vs. IVC+IAC groups, respectively (p=0.030) (24). When BCG is unavailable or patients cannot tolerate BCG, IAC may be a viable option to add to IVC for increased efficacy. Prospective randomized trials are needed to validate IAC use for NMIBC patients.

This survey has several strengths. It is the first survey that assesses the practice patterns of urologists treating BCG-unresponsive NMIBC in Arab countries. It also sheds light on strategies used by urologists and their knowledge about alternative therapies to BCG during the ongoing BCG shortage. This survey has several limitations.

First, the small sample size may indicate that the results may not be representative of all Arab countries due to the low response rate to the survey.

Second, by asking urologists about their patients seen during the last 6 months, a recall bias may exist.

Third, the survey was sent only to urologists. It is unclear whether medical oncologists have a role in the selection of second-line therapy for BCG-unresponsive NMIBC patients. Fourth, selection bias based on prior experience in non-BCG-unresponsive cases might be inappropriately applied by urologists when asked about their preferred therapy.

## CONCLUSIONS

The present survey found that in Arab countries, RC is still highly used for HR BCG-unresponsive NMIBC patients, while there is an emerging role for intravesical chemotherapy. The most preferred chemotherapies used are gemcitabine and MMC. Oncological safety (fear of progression) and the lack of inclusion of specific chemotherapy drugs in their guidelines mostly limit their usage by Arab urologists. While the BCG shortage is still an ongoing problem, Arab

urologists are aware of new evidence emerging on intravesical chemotherapy, especially Gem/Doce, and are willing to utilize those new therapies to cope with the shortage. Novel drugs, which include intravesical and intravenous immunotherapy as well as bacterial and viral intravesical therapies, have shown promising results as alternatives to RC in BCG-unresponsive disease. It is crucial to raise awareness among urologists about these emerging therapies. There is also a need to develop clinical trials for NMIBC in Arab countries and facilitate patient access to these trials to further advance this field.

## REFERENCES

1. Taylor J, Becher E, Steinberg GD. Update on the guideline of guidelines: non-muscle-invasive bladder cancer. *BJU Int.* 2020; 125:197-205.
2. van den Bosch S, Alfred Witjes J. Long-term cancer-specific survival in patients with high-risk, non-muscle-invasive bladder cancer and tumour progression: a systematic review. *Eur Urol.* 2011; 60:493-500.
3. Roumiguié M, Kamat AM, Bivalacqua TJ, et al. International Bladder Cancer Group Consensus Statement on Clinical Trial Design for Patients with Bacillus Calmette-Guérin-exposed High-risk Non-muscle-invasive Bladder Cancer. *Eur Urol.* 2022; 82:34-46.
4. Babjuk M, Burger M, Compérat EM, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ) - 2019 Update. *Eur Urol.* 2019; 76:639-657.
5. Yassaie O, Chehroudi C, Black PC. Novel and emerging approaches in the management of non-muscle invasive urothelial carcinoma. *Ther Adv Med Oncol.* 2021; 13:17588359211039052.
6. Bandari J, Maganty A, MacLeod LC, et al. Manufacturing and the Market: Rationalizing the Shortage of Bacillus Calmette-Guérin. *Eur Urol Focus.* 2018; 4:481-484.
7. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. *J Urol.* 2016; 196:1021-1029.
8. Nazmifard M, Williams C, Naser-Tavakolian A, et al. Clinical and Preclinical Therapies for Bladder Cancer Following Bacillus Calmette-Guérin Failure. *J Urol.* 2023; 209:32-48.
9. Goldberg IP, Lichtbroun B, Singer EA, et al. Pharmacologic Therapies for Non-Muscle Invasive Bladder Cancer: Current and Future Treatments. *Arch Pharmacol Ther.* 2022; 4:13-22.
10. Abou Chakra M, Shore ND, Dillon R, et al. US Clinical Practice Patterns of Intravesical Chemotherapy for Bacillus Calmette-Guérin-Unresponsive and Bacillus Calmette-Guérin-Exposed Nonmuscle-Invasive Bladder Cancer. *Urol Pract.* 2024; 11:97-107. 1.
11. Collacott H, Krucien N, Heidenreich S, et al. Patient Preferences for Treatment of Bacillus Calmette-Guérin-unresponsive Non-muscle-invasive Bladder Cancer: A Cross-country Choice Experiment. *Eur Urol Open Sci.* 2023; 49:92-99.
12. Joudi FN, Smith BJ, O'Donnell MA, et al. Contemporary management of superficial bladder cancer in the United States: a pattern of care analysis. *Urology.* 2003; 62:1083-8.
13. Broughton EI, Gooden KM, Mycock KL, et al. Multi-country clinical practice patterns, including use of biomarkers, among physicians' treatment of BCG-unresponsive non-muscle invasive bladder cancer (NMIBC). *BMC Urol.* 2022; 22:27.
14. Broughton EI, Chun DS, Gooden KM, et al. Treatment and disease management patterns for bacillus Calmette-Guérin unresponsive nonmuscle invasive bladder cancer in North America, Europe and Asia: A real-world data analysis. *Curr Urol.* 2022; 16:147-153.
15. Abou Chakra M, Packiam VT, O'Donnell MA. Real-world efficacy of adjuvant single-agent intravesical gemcitabine for non-muscle invasive bladder cancer (published online ahead of print, 2023 Oct 16). *Expert Opin Pharmacother.* 2023; 1-11.
16. Jarow JP, Lerner SP, Kluetz PG, et al. Clinical trial design for the development of new therapies for nonmuscle-invasive bladder cancer: report of a Food and Drug Administration and American Urological Association public workshop. *Urology.* 2014; 83:262-4.
17. Wettstein MS, Naimark D, Hermanns T, et al. Required efficacy for novel therapies in BCG-unresponsive non-muscle invasive bladder cancer: Do current recommendations really reflect clinically meaningful outcomes?. *Cancer Med.* 2020; 9:3287-3296.
18. Bandari J, Maganty A, MacLeod LC, et al. Manufacturing and the Market: Rationalizing the Shortage of Bacillus Calmette-Guérin. *Eur Urol Focus.* 2018; 4(4):481-484.
19. McElree IM, Steinberg RL, Mott SL, et al. Comparison of Sequential Intravesical Gemcitabine and Docetaxel vs Bacillus Calmette-Guérin for the Treatment of Patients With High-Risk Non-Muscle-Invasive Bladder Cancer. *JAMA Netw Open.* 2023; 6:e230849.
20. Katoue MG, Cerda AA, García LY, Jakovljevic M. Healthcare system development in the Middle East and North Africa region: Challenges, endeavors and prospective opportunities. *Front Public Health.* 2022; 10:1045739.
21. World Bank. GDP Per Capita, PPP (Current International \$). World Development Indicators Database. World Bank, 2023. (<https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD>).
22. Chen J, Yao Z, Qiu S, et al. Comparing intra-arterial chemotherapy combined with intravesical chemotherapy versus intravesical chemotherapy alone: a randomised prospective pilot study for T1G3 bladder transitional cell carcinoma after bladder-preserving surgery. *Cardiovasc Intervent Radiol.* 2013; 36:1521-1526.
23. Huang B, Huang G, Li W, et al. Intra-arterial chemotherapy combined with intravesical chemotherapy compared with intravesical BCG immunotherapy retrospectively in high-risk non-muscle-invasive bladder cancer after transurethral resection of the bladder tumor. *J Cancer Res Clin Oncol.* 2021; 147:1781-1788.
24. Lian F, Chen W, Liu Y, et al. Intra-arterial chemotherapy combined with intravesical chemotherapy is effective in preventing recurrence in non-muscle invasive bladder cancer. *J Cancer Res Clin Oncol.* 2019; 145:1625-1633.

## Correspondence

Mohamad Moussa, MD  
mohamadamoussa@hotmail.com  
Mohamad Abou Chakra, MD (Corresponding Author)  
mabouchakra@uiowa.edu  
University of Iowa, IA, US

Neal D. Shore, MD  
nshore@auclinics.com  
Athanasios Papatsoris, MD  
agpapatsoris@yahoo.gr  
Yasser Farahat, MD  
yasserfarahat@gmail.com  
Michael A O'Donnell, MD  
michael-odonnell@uiowa.edu

**Conflict of interest:** The authors declare no potential conflict of interest.