OPEN

# Effect of Hypertension on Outcomes of High-Risk Patients After BCG-Treated Bladder Cancer

## *A Single-Institution Long Follow-Up Cohort Study*

*Fabrizio Dal Moro, MD, Alberto Bovo, MD, Alessandro Crestani, MD, Roberto Vettor, MD, Marina P. Gardiman, MD, and Filiberto Zattoni, MD*

**Abstract:** Immunotherapy with Bacillus Calmette–Guérin (BCG) is the most efficacious treatment for high-risk bladder cancer (BC) (Ta/T1 or carcinoma in situ) to reduce the risk of recurrence. Our aim was to evaluate whether hypertension and diabetes influence the outcome of patients with noninvasive BC treated with BCG instillations.

In order to collect homogeneous data, we considered as ''hypertensive'' only those patients who had previous diagnosed hypertension and a history of taking medical therapy with antihypertensive drugs (AHT), and as ''diabetic'' only those prescribed oral antidiabetics or insulin (ADT).

We analyzed 343 high-risk BC patients undergoing BCG (1995–2010) with a median follow-up of 116 months (range 48–238). The distribution of various kinds of AHT and antidiabetic drugs was homogeneous, with no significant differences ($p > 0.05$).

In both univariate and multivariate analyses, the only statistically significant parameter prognostic for recurrence after BCG treatment was AHT. Recurrence-free survival curves showed a significant correlation with AHT ($p = 0.0168$, hazards ratio [HR] 1.45, 95% confidence interval [CI] 1.0692–1.9619); there was no correlation ($p = 0.9040$) with ADT (HR 0.9750, 95% CI 0.6457–1.4721). After stratification of AHT and ADT according to drug(s) prescribed, there were no significant differences in the BC recurrence rate ($p > 0.05$).

In this study with a very long-term follow-up, hypertension alone (evaluated by AHT) revealed the increased risk of BC recurrence after BCG treatment.

Several hypotheses have been formulated to support these findings, but further prospective studies are needed to both evaluate the real influence of hypertension and identify a possible prognostic factor to be used in selecting poor-prognosis BC patients as early candidates for surgical treatment.

(*Medicine* 94(9):e589)

**Abbreviations**: ADT = oral antidiabetics or insulin, AHT = antihypertensive drugs, BC = bladder cancer, BCG = Bacillus Calmette–Guérin, HDL = high-density lipoprotein, MetS = metabolic syndrome.

Editor: Muhammed Mubarak.
Received: November 24, 2014; revised: February 3, 2015; accepted: February 4, 2015.
From the Department of Surgical, Oncological and Gastroenterological Sciences-Urology (FDM, AB, AC, FZ); Department of Medicine DIMED (RV), Metabolic Diseases and Cardiovascular Risk Unit; and Department of Pathology (MPG), Azienda Ospedaliera di Padova, Padova, Italy.
Correspondence: Fabrizio Dal Moro, Department of Surgical, Oncological and Gastroenterological Sciences, University of Padova, Via Giustiniani 2, 35128 Padova, Italy (e-mail: fabrizio.dalmoro@unipd.it).
The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000589

## INTRODUCTION

The components of the metabolic syndrome (MetS) have been individually and/or cumulatively linked to the risk of cancer.[1] The mechanism underlying these associations is unknown, although experimental and clinical studies indicate the possible involvement of various biological processes.[2]

One problem in interpreting the results of published studies on the correlation between MetS and cancer is often the nonstandardized definition of MetS. The different weights assigned to each MetS component may also generate different hierarchical distributions, resulting in noncomparable data.

In 2003, the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) developed a definition of MetS, which required 3 or more of the following 5 factors to be present: increased waist circumference (102/88 cm for men and women, respectively), hypertriglyceridemia (≥8.33 mmol/L), low high-density lipoprotein (HDL) cholesterol (<2.22 and 2.78 mmol/L for men and women), hypertension (≥130/85 mm Hg), and elevated fasting glucose (≥5.5 mmol/L).[3]

Although the influence of MetS on the development of several cancers (colorectal, pancreas, liver, and breast) has been extensively reported, there are few data on the association between MetS and the risk of bladder cancer (BC), for both separate components and MetS factors combined.

Starting from the NCEP-ATP III definition, we first carried out a retrospective cohort study (unpublished data) on the influence of MetS on BC, demonstrating no significant correlation between BC and body mass index (instead of waist circumference), triglyceridemia, HDL-cholesterol, hypertension ($p = 0.7866$) or hyperglycemia ($p = 0.6064$).

We then focused on the group of patients with noninvasive high-risk BC treated with instillations of Bacillus Calmette–Guérin (BCG), examining several parameters, such as age, as predictors of the response to immunotherapy.

According to European Association of Urology guidelines, BCG is the most efficacious treatment for high-risk BC (Ta/T1 or carcinoma in situ) to reduce the risk of recurrence.[4] Its mechanism of action continues to be poorly defined, but it has been shown to involve a T-helper type 1 immunomodulatory response.

In order to collect homogeneous data, we did not directly examine 2 of the components of MetS (hypertension and diabetes) but antihypertensive (AHT) and antidiabetic (ADT) therapies. Our aim was to determine whether AHT and ADT, alone or in combination, could influence the response to BCG therapy in patients with noninvasive BC.

## METHODS

From 1995 to 2010, we conducted a retrospective cohort study on patients with diagnosed noninvasive high-risk BC, treated with BCG instillations according to the standard scheme of 6-weekly instillations (induction) and then 6-monthly ones (maintenance cycle). We used a low BCG dose (27 mg), as reported in our clinical study demonstrating the efficacy of this low dosage, with significantly reduced side effects.[5]

Of the above components of MetS, we analyzed (alone or in combination) only hypertension and diabetes but, for homogeneous data, we considered as "hypertensive" only those patients who had previous diagnosed hypertension and a history of taking medical therapy with AHT, and as "diabetic" only those prescribed ADT.

We analyzed BC clinical stages (TNM classification) and grading (G1, G2, G3; WHO, 1973) before BCG treatment, recording data relating to BC follow-up, with cystoscopy and urinary cytology, after the first 6-weekly instillation, after the 6-monthly instillations, and during the further follow-up (until March 2014). The finding of BC (any T, any G) during cystoscopy and/or positive urinary cytology was defined as "recurrent disease."

### Ethical Approval

Ethical approval was not necessary in this retrospective study.

### Statistics

The McNemar test for univariate analysis was used to compare categorical variables in the 2 groups. Cox multivariate regression model was used to compare time-independent variables. Recurrence-free data, considered as survival data, were estimated with the Kaplan–Meier method and compared with the log-rank test. Statistical significance was set at $p < 0.05$. All analyses were performed with (MedCalc Software, Ostend, Belgium) for Windows, version 13.1.

## RESULTS

A total of 343 consecutive patients was analyzed, 293 men and 50 women. The distribution of the various AHT and antidiabetic drugs was homogeneous, without significant differences ($p > 0.05$).

We found a significant correlation between AHT and ADT and initial staging/grading of BC ($p = 0.0185$ and $P = 0.0147$, respectively), as shown in Table 1.

Median follow-up was 116 months (range 48–238), during which recurrence of disease after BCG treatment was recorded in 137 patients (39.9%). Patient characteristics and stratification according to AHT and ADT relating to recurrence of disease after BCG treatment are listed in Table 2.

Analysis of the risk of recurrence, according to both MetS components evaluated, showed that ADT patients had a 43.5% of risk of developing new BC after BCG treatment, whereas non-ADT patients had a risk of 39.4% ($p = 0.5990$, odds ratio [OR] = 1.18, 95% confidence interval [CI] 0.6317–2.2169). The risk of recurrence for AHT patients was 48.4% but only 34.9% in non-AHT patients ($p = 0.0136$, OR = 1.75, 95% CI 1.1227–2.7388). When AHT and ADT patients were grouped together, no significant differences were found ($p = 0.3904$). According to the AHT parameter, the recurrence-free survival curves showed a significant correlation ($p = 0.0168$, hazards ratio [HR] 1.45, 95% CI 1.0692–1.9619) (Figure 1) but none with the ADT parameter ($p = 0.9040$, HR 0.9750, 95% CI 0.6457–1.4721). After stratification of AHT and ADT according to drug, there were no significant differences in the BC recurrence rate ($p > 0.05$). Stratifying AHT, we found that in the group of 40 patients treated with angiotensin-converting enzyme inhibitors, 21 (52.5%) had BC recurrence and 19 (47.5%) no recurrence; of the 27 cases taking diuretics, 12 (44.4%) had a recurrence and 15 (55.4%) did not. In the group of 20 patients

**TABLE 1.** Patients' Characteristics and Distribution of BC Grading According to Therapy

| **Patients' Characteristics** | | | | |
|---|---|---|---|---|
| **Gender** | **Male** | **%** | **Female** | **%** |
| | 293 | 85.4 | 50 | 14.6 |
| Therapy | AHT (%): 128 (37.3) | No AHT (%): 215 (62.7) | ADT (%): 46 (13.4) | No ADT (%): 297 (86.6) |
| Grading | G0–G2: 230 | 67 | G3: 113 | 33 |

**Distribution of BC Grading According to Therapy**

| | **Grading** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **G0–G2** | **%** | **G3** | **%** | ***p* Value*** | **OR** | **95% CI** |
| Therapy | | | | | | | |
| AHT | 75 | 32.6 | 53 | 46.9 | 0.0105 | 0.5478 | 0.3455–0.8686 |
| No AHT | 155 | 67.4 | 60 | 53.1 | | | |
| ADT | 22 | 9.6 | 24 | 21.2 | 0.0147 | 0.4583 | 0.2449–0.8578 |
| No ADT | 198 | 90.4 | 99 | 78.8 | | | |

ADT = antidiabetic therapy, AHT = antihypertensive therapy, BC = bladder cancer, CI = confidence interval, OR = odds ratio.
* McNemar test.

**TABLE 2.** Outcomes after BCG treatment

| | Recurrence | % | No Recurrence | % | *p* Value* | OR | 95% CI |
|---|---|---|---|---|---|---|---|
| AHT | 62 | 48.4 | 66 | 51.6 | **0.0136** | 1.75 | 1.1227–2.7388 |
| No AHT | 75 | 34.9 | 140 | 65.1 | | | |
| ADT | 20 | 43.5 | 26 | 56.5 | 0.5990 | 1.18 | 0.6317–2.2169 |
| No ADT | 117 | 39.4 | 180 | 60.6 | | | |
| AHT + ADT | 13 | 41.9 | 18 | 58.1 | 0.3904 | 1.402 | 0.6484–3.0311 |
| No AHT + No ADT | 68 | 34 | 132 | 66 | | | |

ADT = antidiabetic therapy, AHT = antihypertensive therapy, BCG = Bacillus Calmette–Guérin, CI = confidence interval, OR = odds ratio.
* McNemar test.

with hypertension treated with β-blockers, 9 (45%) had BC recurrence and 55% (11) did not; of 14 patients using a calcium channel blocker, 6 (42.9%) had a recurrence and 8 (57.1%) did not; in the 27 patients taking a combination of drugs or other medications, the distribution was 14 cases (51.8%) in the group with BC recurrence and 13 (48.2%) in the other group ($p > 0.05$).

In multivariate analysis (Table 3), the only statistically significant parameter prognostic for recurrence after BCG treatment was AHT ($p = 0.0185$).

## DISCUSSION

Despite the clear demonstration of a relation between MetS and cancer, there are few data on the association between MetS and the specific risk of BC. A recent large prospective study showed that MetS is associated with a significant, albeit modest, increase in BC risk in men, without evidence of synergy among various MetS factors.[6] The data showed that, among single MetS components, only hypertension was significantly associated with risk in men; among women with high glucose, there was a nonsignificant increase in risk. Other less extensive studies have reported no associations.[1]

In our experience, we confirm (Dal Moro, 2012) that there is no association among hypertension, diabetes and BMI, and BC.

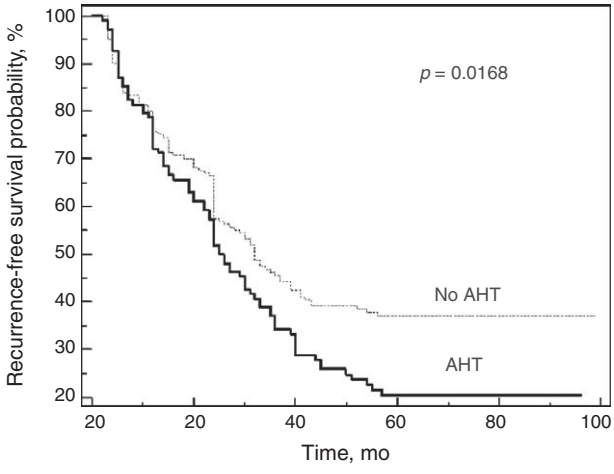


**FIGURE 1.** Kaplan–Meier recurrence-free survival among patients with high-risk BC BCG-treated with AHT. AHT = antihypertensive therapy, BC = bladder cancer.

The role of hypertension in the development of cancer is under controversial discussion, because several authors have reported discordant results.[7] In 1991, Grove et al[8] analyzed a large population in a 20-year prospective study and demonstrated that there was no association between systolic and diastolic blood pressure and total cancer incidence or death due to cancer. However, another prospective study with a 14-year follow-up found that both systolic and diastolic blood pressures were significantly associated with subsequent mortality from cancer (lung, colon, and all other sites combined).[9]

Several other prospective studies have provided evidence indicating that hypertension in itself represents a significant risk for malignancies, and the organ most frequently involved, even in long-term prospective studies, is the kidney.[10] However, little is known about possible pathways between hypertension and cancer.[11]

Some authors have suggested that AHT medications are responsible for the excess mortality, although the effects of such drugs on decreasing cardiovascular morbidity and mortality have been extensively demonstrated.[12] A review by Grossman et al[13] revealed that only diuretics seem to be carcinogenic for renal cell carcinoma (risk ratio 1.55), whereas the association between other AHT and malignancy was absent or even inverse (the case of calcium antagonists).

In our series of hypertensive patients, there was a nonsignificant correlation between BC and various kinds of AHT and ADT, which meant that the variable ''specific drug'' could not be evaluated.

The aim of our study was to analyze only a group of high-risk BC patients treated with BCG, in order to evaluate the influence of hypertension and diabetes on the response to immunotherapy.

The mechanism of action of BCG therapy is not completely understood: the live attenuated strain of *Mycobacterium bovis* instilled into the bladder induces the same type of histologic and immunologic reaction as that found in patients with tuberculosis. After being processed by macrophages, some fragments combine with histocompatibility antigens and appear on the cell surface, where they stimulate $CD4^+$ T cells and induce a primarily T-helper type 1 immune response, which targets these cells for destruction. For BCG to be effective, the host should be immunocompetent.

We demonstrate that patients with a history of taking drugs to control hyperglycemia are not at risk of BC recurrence after BCG treatment. Conversely, AHT seems to be related to a significantly higher risk of such recurrence than in patients with no history of hypertension or use of AHT, with no differences concerning sex, age or grading of cancer.[14]

**TABLE 3.** Multivariate Analysis

| Independent Variable | Coefficient | Standard Error | *t* | *p* Value* |
|---|---|---|---|---|
| Age at onset | −0.002567 | 0.002591 | −0.991 | 0.3225 |
| ADT | 0.01226 | 0.08007 | 0.153 | 0.8784 |
| AHT | −0.1482 | 0.05758 | −2.574 | **0.0185** |
| Grading | 0.01903 | 0.02284 | 0.833 | 0.4054 |

ADT = antidiabetic therapy, AHT = antihypertensive therapy.
* Cox multivariate regression model.

The relationship between blood pressure (and AHT) and cancer may differ according to follow-up time: in our experience, considering the Kaplan–Meier curve related to AHT, the gap between the 2 recurrence-free survival curves widens after 22 months. In the literature, 1 prospective study demonstrated that only after 5 years of follow-up was there a positive association between systolic (but not diastolic) blood pressure and risk of cancer mortality.[15]

Our study has certain strengths. First, the number of cases analyzed is high, considering patient characteristics (BCG-treated BC). Second, the follow-up is impressive (from 4 to 19 years) and higher than other studies in the literature reporting similar values. Third, as a single-center study, we excluded possible bias in pathological analysis, because all histological samples were analyzed by the same pathologist (M.P.G.).

This study also has some limitations. The first is its retrospective characteristic, although all data were extracted from our medical records; therefore, the possibility of selection bias cannot be excluded. Second, we did not consider ''hypertension'' but ''antihypertensive therapy''. The same applies to ''diabetes'' and ''antidiabetic therapy'', which are not properly components of MetS. However, this choice did allow us to standardize these parameters. In many published reports, although the definition of ''hypertension'' is correct and standardized, it is possible that some false-positive patients were included, in whom the recorded high blood pressure was only a temporary alteration, perhaps due to the effect of hospitalization.

Therefore, we cannot state definitely that the higher risk of recurrence in hypertensive (treated) patients in comparison with nonhypertensive ones is correlated primarily to hypertension or AHT, although the distribution of the various kinds of drugs makes this parameter nonsignificant.

## Hypotheses

Considering the possible role of ''hypertension'' we can propose some hypotheses.

We speculate that, when BCG treatment is ineffective, an inadequate immunitary response is at work, perhaps caused by several factors: first, blood pressure elevation has been demonstrated to determine micro- (and macro-) vascular alterations (such as atherosclerosis), giving rise to insufficient blood supply and modifying the immunologic reaction to BCG. Second, the proven relation between inflammation and hypertension, through the activation of Th1 cells and the production of neoantigens, may play a role in the altered immunitary response to BCG.[16] Innate and adaptive immune responses may contribute to this process, as alterations of the immune response have been implicated in the genesis of hypertension, as demonstrated in several studies focusing on the possible role of immune perturbations.[17]

## CONCLUSIONS

The mechanisms involving the immune response to BCG in hypertensive BC patients treated with BCG are still elusive, and the findings of the present study may represent an interesting starting point for further prospective studies, to evaluate both the real influence of hypertension and to identify a possible prognostic factor to be used in selecting poor-prognosis BC patients as early candidates for surgical treatment.

To the best of our knowledge, no previous studies have focused on the effects of single components of MetS and/or specific therapies in relation to BC recurrence risk after BCG therapy.

## ACKNOWLEDGMENTS

*None.*

## REFERENCES

1. Esposito K, Chiodini P, Colao A, et al. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care.* 2012;35:2402–2411.
2. Hursting SD, Hursting MJ. Growth signals, inflammation, and vascular perturbations: mechanistic links between obesity, metabolic syndrome, and cancer. *Arterioscler Thromb Vasc Biol.* 2012;32:1766–1770.
3. Lipsy RJ. The National Cholesterol Education Program Adult Treatment Panel III guidelines. *J Manag Care Pharm.* 2003;9:2–5.
4. Kawai K, Miyazaki J, Joraku A, et al. Bacillus Calmette–Guérin (BCG) immunotherapy for bladder cancer: current understanding and perspectives on engineered BCG vaccine. *Cancer Sci.* 2013;104:22–27.
5. Pagano F, Bassi P, Milani C, et al. A low dose Bacillus Calmette–Guérin regimen in superficial bladder cancer therapy: is it effective? *J Urol.* 1991;146:32–34.
6. Häggström C, Stocks T, Rapp K, et al. Metabolic syndrome and risk of bladder cancer: prospective cohort study in the metabolic syndrome and cancer patients (Me-Can). *Int J Cancer.* 2011;128:1890–1898.
7. Rosengren A, Himmelmann A, Wilhelmsen L, et al. Hypertension and long-term cancer incidence and mortality among Swedish men. *J Hypertens.* 1998;16:933–940.
8. Grove JS, Nomura A, Severson RK, et al. The association of blood pressure with cancer incidence in a prospective study. *Am J Epidemiol.* 1991;134:942–947.
9. Dyer AR, Stamler J, Berkson DM, et al. High blood-pressure: a risk factor for cancer mortality? *Lancet.* 1975;1:1051–1056.

10. Schmieder RE, Delles C, Messerli FH. Diuretic therapy and the risk for renal cell carcinoma. *J Nephrol.* 2000;13:343–346.
11. Stumpe KO. Hypertension and the risk of cancer: is there new evidence? *J Hypertens.* 2002;20:565–567.
12. Chow WH, McLaughlin JK, Mandel JS, et al. Risk of renal cell cancer in relation to diuretics, antihypertensive drugs, and hypertension. *Cancer Epidemiol Biomarkers Prev.* 1995;4:327–331.
13. Grossman E, Messerli FH, Goldbourt U. Does diuretic therapy increase the risk of renal cell carcinoma? *Am J Cardiol.* 1999;83:1090–1093.
14. Dal Moro F, Rossi A, Zattoni F. Does age really matter in the choice of treatment for bladder cancer? *Br J Cancer.* 2013;108:2415–2416.
15. Wannamethee G, Shaper AG. Blood pressure and cancer in middle-aged British men. *Int J Epidemiol.* 1996;25:22–31.
16. Zweifach BW. The microcirculation in experimental hypertension. State-of-the-art review. *Hypertension.* 1983;5:I10–I16.
17. Harrison DG, Guzik TJ, Lob HE, et al. Inflammation, immunity, and hypertension. *Hypertension.* 2011;57:132–140.