EXPERIENCIA CON INSTILACIONES INTRAVESICALES DE BCG EN PACIENTES CON CANCER VESICAL NO MÚSCULO INVASIVO EN EL COMPLEJO HOSPITALARIO UNIVERSITARIO DE BADAJOZ EN EL PERIODO 2012-2017.

Mario Paúl Sánchez Pérez

Complejo Hospitalario Universitario de Badajoz

Cáncer de vejiga

- 7° neoplasia más diagnosticada en hombres, 17° en mujeres y 11° en ambos géneros.
- Incidencia estandarizada por edad 9 para hombres y 2.2 para mujeres por 100000/personas/año.
- En España se diagnostican aproximadamente 20000 casos/año. Incidencia de 24,4 casos nuevos por 100.000 habitantes/año y de 17,8 casos recidivados por 100.000 habitantes/año.
- 75% de los nuevos diagnósticos corresponden a tumores no músculo invasivos.

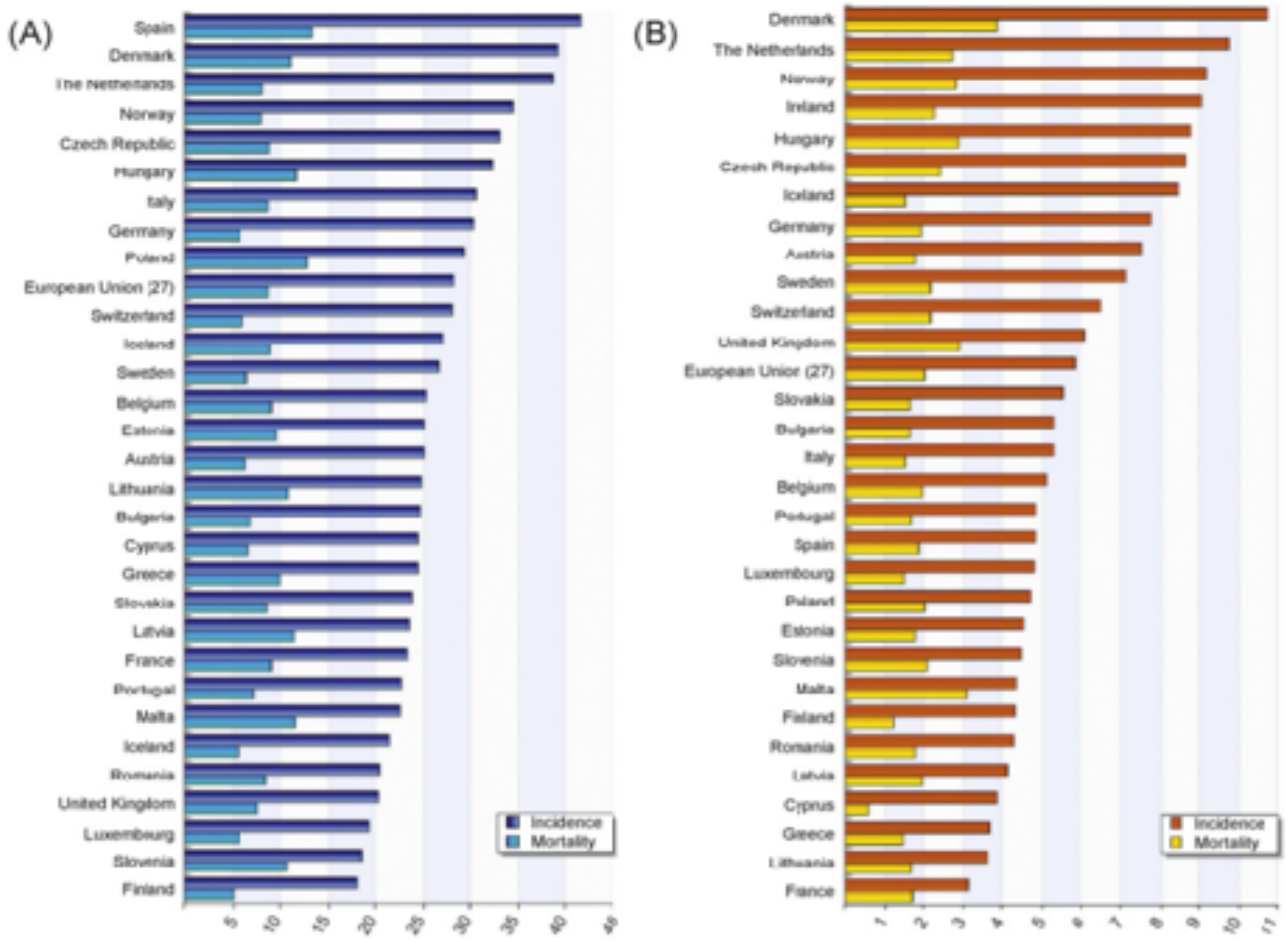
-Ferlay J., et al, Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86. doi: 10.1002/ijc.29210. Epub 2014 Oct 9.

-Burger, M., et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol, 2013. 63: 234.

-Siegel RL, Miller KD, Jemal A. **Cancer Statistics, 2017. CA Cancer J Clin. 2017 Jan;67(1):7-30. doi: 10.3322/caac.21387. Epub 2017 Jan 5.**

-Miñana B, et al. Bladder cancer in Spain 2011: population based study. J Urol. 2014 Feb;191(2):323-8. doi: 10.1016/j.juro.2013.08.049. Epub 2013 Aug 28. PubMed PMID: 23994371.

Cáncer vesical



Taba1. Tasas estimadas estandarizadas por edad de incidencia y mortalidad de cáncer vesical por 100000 personas/año en hombres (A) y mujeres (B). Estudio GLOBOCAN (1). Disponible en: http://globocan.iarc.fr.

Clasificación y estadificación Cáncer Vesical

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant metastasis	
M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastases

1973 WHO grading

Grade 1: well differentiated

Grade 2: moderately differentiated

Grade 3: poorly differentiated

2004 WHO grading system (papillary lesions)

Papillary urothelial neoplasm of low malignant potential (PUNLMP)

Low-grade (LG) papillary urothelial carcinoma

High grade (HG) papillary urothelial carcinoma

Tabla 2. TNM classification of malignant tumors. UICC International Union Against Cancer. 8th edn. 2016 (4). Disponible en: http://uroweb.org.

Tratamiento Cáncer vesical no músculo invasivo

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG), < 3 cm, no CIS	One immediate instillation of intravesical chemotherapy after TURB.
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high-risk).	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score < 5, one immediate instillation of intravesical chemotherapy after TURB. In all patients either one-year full-dose BCG treatment (induction plus three-weekly instillations at three, six and twelve months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year.
High-risk tumours	Any of the following: • T1 tumours; • G3 (HG) tumour; • CIS; • Multiple, recurrent and large (> 3 cm) TaG1G2/LG tumours (all features must be present).	Intravesical full-dose BCG instillations for one-three years or radical cystectomy (in highest-risk tumours - *see below*).
	Subgroup of highest-risk tumours	
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, LVI (see Sections 4.7 and 6.4).	Radical cystectomy should be considered. In those who refuse or are unfit for RC intravesical full-dose BCG instillations for one-three years.
	BCG failure.	Radical cystectomy is recommended.

Treatment recommendations in TaT1 tumours and carcinoma *in situ* according to risk stratification. Non-muscle-invasive Bladder Cancer. EAU Guidelines. Disponible en: http://uroweb.org

Tratamiento Cáncer vesical no músculo invasivo

Risk category	Definition	Treatment recommendation
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG), < 3 cm, no CIS	One immediate instillation of intravesical chemotherapy after TURB.
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high-risk).	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score < 5, one immediate instillation of intravesical chemotherapy after TURB. In all patients either one-year full-dose BCG treatment (induction plus three-weekly instillations at three, six and twelve months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year.
High-risk tumours	Any of the following: • T1 tumours; • G3 (HG) tumour; • CIS; • Multiple, recurrent and large (> 3 cm) TaG1G2/LG tumours (all features must be present).	Intravesical full-dose BCG instillations for one-three years or radical cystectomy (in highest-risk tumours - *see below*).
	Subgroup of highest-risk tumours	
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, LVI (see Sections 4.7 and 6.4).	Radical cystectomy should be considered. In those who refuse or are unfit for RC intravesical full-dose BCG instillations for one-three years.
	BCG failures.	Radical cystectomy is recommended.

Treatment recommendations in TaT1 tumours and carcinoma *in situ* according to risk stratification. Non-muscle-invasive Bladder Cancer. EAU Guidelines. Disponible en: http://uroweb.org

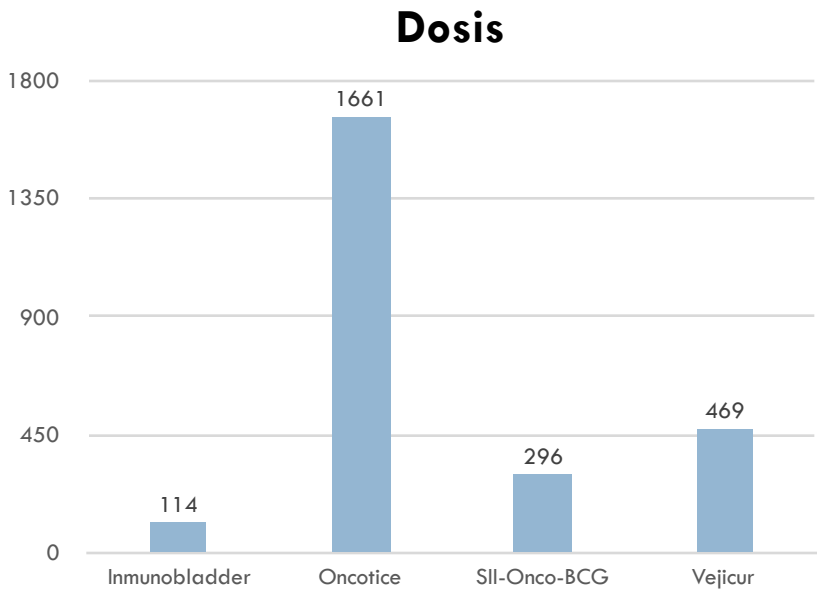
Bacilo de Calmette-Guerin

- 1904 Novard aisla Micobacterium Bovis.
- 1908-1920 Bacillus Clamette-Guerin.
- 1976 Dr. Álvaro Morales describe el primer tratamiento exitoso con BCG en pacientes con Cáncer de vejiga.
- Mecanismos efectores: actividad antitumoral de interferones y células "BAK" (BCG Activated Killer).

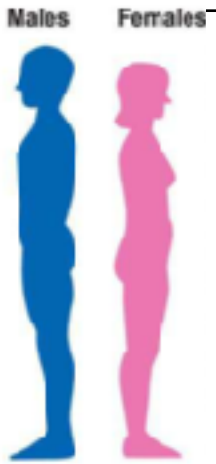
Suttmann H[1], Jacobsen M, Reiss K, Jocham D, Böhle A, Brandau S. Mechanisms of bacillus Calmette-Guerin mediated natural killer cell activation. Send to J Urol. **2004 Oct;172(4 Pt 1):1490-5.**

Experiencia con instilaciones intravesicales de BCG en CHUB, periodo 2012-2017.

- 260 pacientes, 2540 dosis administradas.
  - Media de 9,76 dosis por persona (+/-1,73SD).
- Mediana de edad al diagnóstico 71 años (45-92).
- Mediana de seguimiento de 37 meses.



Inmunobladder		
Oncotice	Cepa TICE	2-8 x 10^8 UFC
SII-Onco-BCG	Cepa BCG 1-361	1-19,2 x 10^8 UFC
Vejicur	Cepa RIVM	2 x 10^8 - 3 x 10^9 UFC



Hombres 228 (87,69%)

Mujeres 32 (12,3%)

Experiencia con instilaciones intravesicales de BCG en CHUB, periodo 2012-2017.

- Pauta:
  - Inducción: 1 dosis semanal x 6 semanas.
  - Mantenimiento: 1 dosis semanal x 3 semanas a los 3, 6, 12, 18, 24, 30, 36.

- Se utilizó un tercio de dosis o solo se administró dosis de inducción en parte del periodo estudiado.

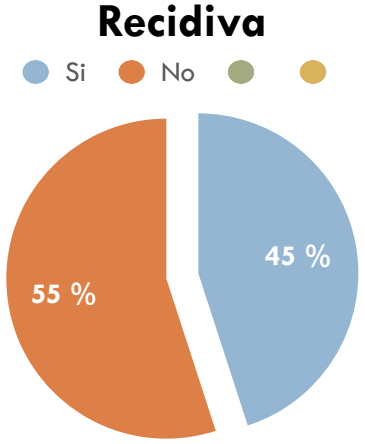
Experiencia con instilaciones intravesicales de BCG en CHUB, periodo 2012-2017.

	Pacientes	%
Tamaño		
<3 cm	116	44,61
>3cm	124	47,69
No especificado	20	7,69
CIS concomitante		
Si	23	8,84
No	237	91,15
Género		
Masculino	228	87,69
Femenino	32	12,3
Número de tumores		
1	123	47,3
2-3	77	29,61
4-7	38	14,61
8 o más	4	1,53
No especificado	18	6,92
Grado OMS 1973		
G1	30	11,53
G2	4	1,53
G3	226	86,92
Estadio T		
Ta	62	23,84
T1	187	71,92
CIS	7	2,69

Fumador	%
Si	60,10%
No	11,17%
No especifica	28,20%

Experiencia con instilaciones intravesicales de BCG en CHUB, periodo 2012-2017.

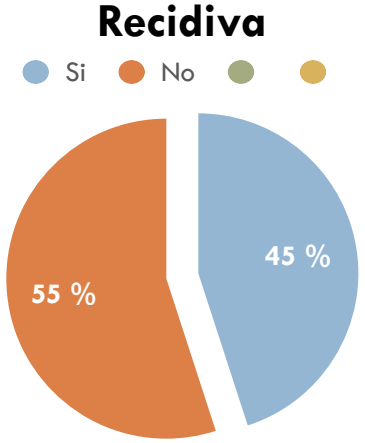
- 45% de los pacientes presentaron al menos un episodio de recidiva.
- Media de 3,27 episodios por paciente que recidiva.
- El tiempo medio desde el inicio del tratamiento hasta la primera recidiva fue de 12 meses (2-120).



	CHUB
1 año	23,07%
2 años	35,76%
5 años	42,30%

Experiencia con instilaciones intravesicales de BCG en CHUB, periodo 2012-2017.

- 45% de los pacientes presentaron al menos un episodio de recidiva.
- Media de 3,27 episodios por paciente que recidiva.
- El tiempo medio desde el inicio del tratamiento hasta la primera recidiva fue de 12 meses (2-120).



	CHUB	EORTC
1 año	23,07%	25,9%
2 años	35,76%	
5 años	42,30%	41,3%

Cambier S., et al. EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guérin. Eur Urol. 2016 Jan;69(1):60-9. doi: 10.1016/j.eururo.2015.06.045. Epub 2015 Jul 23.

Experiencia con instilaciones intravesicales de BCG en CHUB, periodo 2012-2017.

- Al 36,15% se administró 12 instilaciones o más.
- La progresión a cáncer vesical músculo invasivo fue del 10,76%.
- Se reportan 31 (11,92%) casos de efectos adversos asociados al tratamiento, con un caso de fallecimiento (hepatitis granulomatosa).
- Fallecen 58 pacientes durante el seguimiento (22,3%), 19 de ellos por eventos relacionados a su cáncer vesical.

Conclusiones

- Enfermedad de alta prevalencia, y que precisa dedicar recursos para diagnóstico, tratamiento y seguimiento.
- En nuestro centro los datos con respecto a la literatura son similares en cuanto a recidiva, progresión y complicaciones.
- Baja proporción de cumplimiento del protocolo que utilizamos, ya sea por falta de tolerancia al tratamiento, por el desabastecimiento mundial en parte del periodo estudiado.

Referencias Bibliográficas

- Babjuk M., et al. EAU guidelines on non–muscle-invasive urothelial carcinoma of the bladder: update 2016. *European urology*, 2017, vol. 71, no 3, p. 447-461.
- Ferlay J., et al, Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86. doi: 10.1002/ijc.29210. Epub 2014 Oct 9.
- Burger, M., et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol, 2013. 63: 234.
- Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women [published correction appears in JAMA 2011; 306:2220]. JAMA 2011;306:737–45.
- Sobin LH, G.M., Wittekind C., TNM classification of malignant tumors. UICC International Union Against Cancer. 7th edn. 2009, Wiley-Blackwell.
- Suttmann H[1], Jacobsen M, Reiss K, Jocham D, Böhle A, Brandau S. Mechanisms of bacillus Calmette-Guerin mediated natural killer cell activation. Send to J Urol. 2004 Oct;172(4 Pt 1):1490-5.
- Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017 Jan;67(1):7-30. doi: 10.3322/caac.21387. Epub 2017 Jan 5.
- Miñana B, Cózar JM, Palou J, Unda Urzaiz M, Medina-Lopez RA, Subirá Ríos J, de la Rosa-Kehrmann F, Chantada-Abal V, Lozano F, Ribal MJ, Rodríguez Fernández E, Castiñeiras Fernández J, Concepción Masip T, Requena-Tapia MJ, Moreno-Sierra J, Hevia M, Gómez Rodríguez A, Martínez-Ballesteros C, Ramos M, Amón Sesmero JH, Pizá Reus P, Bohorquez Barrientos A, Rioja Sanz C, Gomez-Pascual JA, Hidalgo Zabala E, Parra Escobar JL, Serrano O. Bladder cancer in Spain 2011: population based study. J Urol. 2014 Feb;191(2):323-8. doi: 10.1016/j.juro.2013.08.049. Epub 2013 Aug 28. PubMed PMID: 23994371.
- Sylvester RJ, et al. Predicting Recurrence and Progression in Individual Patients with Stage Ta T1 Bladder Cancer Using EORTC Risk Tables: A Combined Analysis of 2596 Patients from Seven EORTC Trials. European Urology 49: 466 - 477, 2006.
- Cambier S., et al. EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guérin. Eur Urol. 2016 Jan;69(1):60-9. doi: 10.1016/j.eururo.2015.06.045. Epub 2015 Jul 23.
- Gontero P, et al. **Prognostic factors and risk groups in T1G3 non-muscle-invasive bladder cancer patients initially treated with Bacillus Calmette-Guérin: results of a retrospective multicenter study of 2451 patients.** Eur Urol. 2015 Jan;67(1):74-82. doi: 10.1016/j.eururo.2014.06.040. Epub 2014 Jul 16.


GRACIAS