Universidad Rey Juan Carlos

Facultad de Ciencias de la Salud

Departamento de Medicina y Cirugía, Psicología, Medicina Preventiva y Salud

Pública e Inmunología Microbiología Médica y Enfermería y Estomatología

INDIVIDUALIZACIÓN DEL TRATAMIENTO EN EL TUMOR VESICAL NO MÚSCULO-INVASIVO SEGÚN CRITERIOS CLÍNICOS Y ANATOMOPATOLÓGICOS

TESIS DOCTORAL

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Madrid, 2017

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CERTIFICA

Que el proyecto de tesis doctoral titulado "Individualización del tratamiento en el tumor vesical no músculo-invasivo según criterios clínicos y anatomopatológicos", ha sido realizado bajo mi dirección por Dña. Virginia Hernández Cañas, y reúne todos los requisitos científicos y formales para ser presentado y defendido ante el tribunal correspondiente

Y para que así conste a todos los efectos, firmo el presente certificado en Madrid, a dieciséis de enero de dos mil diecisiete

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LISTA DE ABREVIATURAS Y ACRÓNIMOS

AJCC-TNM	American Joint Commitee on Cancer tumor-node-metastatis
AS	Active surveillance
AUC	Area under curve
BCG	Bacilo Calmette-Guérin
BTA	Bladder tumor antigen
CI	Confidence interval
CIF	Cumulative incidence function
CIS	Carcinoma in situ
CUETO	Club Urológico Español de Tratamiento Oncológico
EORTC	European Organisation for Research and Treatment of Cancer
HR	Hazard ratio
IQR	Interquartile range
MMC	Mitomycin C
NMIBC	Non-muscle invasive bladder cancer
OR	Odd Ratio
ROC	Receiver-operating characteristic
SD	Standard deviation
TCGA	The Cancer Genome Atlas
TUR	Transurethral resection
TURBT	Transurethral resection of bladder tumour

ÍNDICE

INTRODUCCIÓN

1. INTRODUCCIÓN

1.1. Epidemiología del cáncer de vejiga

El tumor vesical es el séptimo tumor más frecuente en varones en todo el mundo, y el cuarto en frecuencia dentro del entorno europeo por detrás del cáncer de próstata, el cáncer de pulmón y el cáncer colorrectal [1,2]. Se estima que 5,4 millones de personas en los países más desarrollados y 6,7 millones en los países en vías de desarrollo lo padecen, y las previsiones apuntan a que estas cifras aumentarán en los próximos años[3].

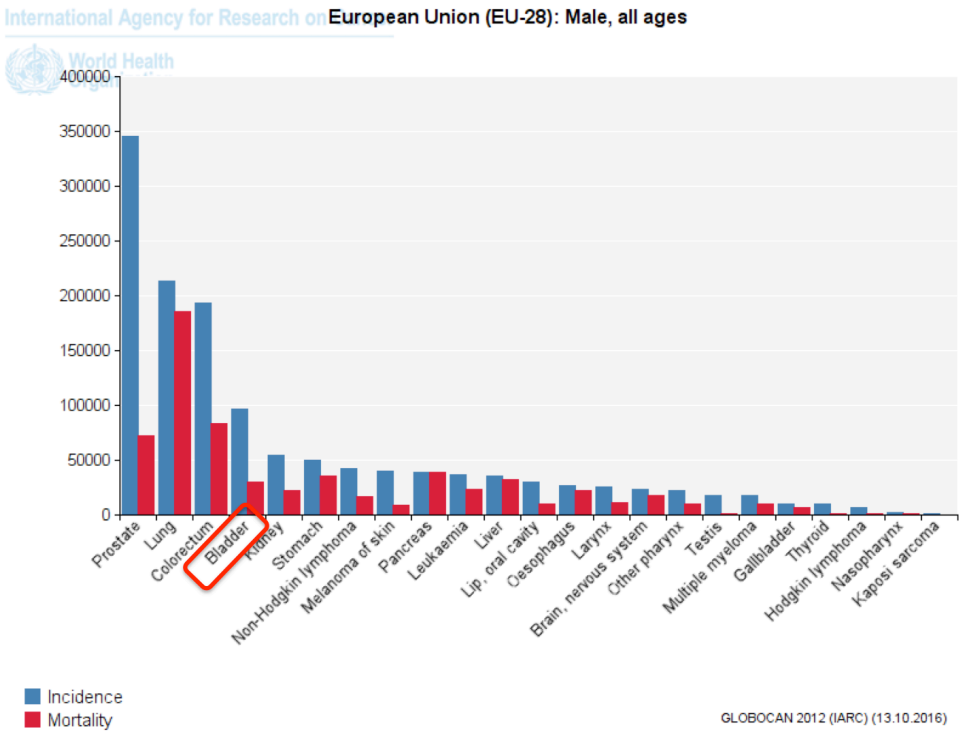

***Figura 1**: Tasas de incidencia y mortalidad de los distintos tipos de tumores en la Unión Europea ordenados según su incidencia de manera decreciente*[1].

En los países desarrollados se está evidenciando actualmente una disminución tanto en los diagnósticos de tumor vesical como en la mortalidad de la enfermedad [4]. Esto es

debido fundamentalmente a dos hechos importantes relacionados con los factores de riesgo conocidos más importantes en el cáncer vesical como son el tabaco y las exposiciones ocupacionales a agentes cancerígenos como las aminas aromáticas. En las últimas décadas, gracias a las políticas sanitarias, se ha producido una disminución progresiva del hábito tabáquico. La prevalencia de fumadores en Europa empezó a disminuir en los años 50 en los varones y a mediados de los 70 en las mujeres. A esto se le suma que las mejores condiciones laborales de los trabajadores han disminuido de forma muy importante la exposición a agentes cancerígenos en el entorno laboral[3].

Sin embargo, a pesar de los factores expuestos anteriormente, existe un hecho relevante que contrarrestará negativamente la disminución en la incidencia de esta patología, y es el envejecimiento de la población. Las pirámides poblacionales se están invirtiendo en todos los países desarrollados, incluido España, y esto traerá consigo un inevitable aumento de toda la patología oncológica entre la que se encuentra el tumor vesical [3]. En concreto, en nuestro país se estima que en 50 años residirán 15,8 millones de personas mayores de 64 años, lo que supone un aumento de un 87,5% de esta franja poblacional con respecto al momento presente[5].

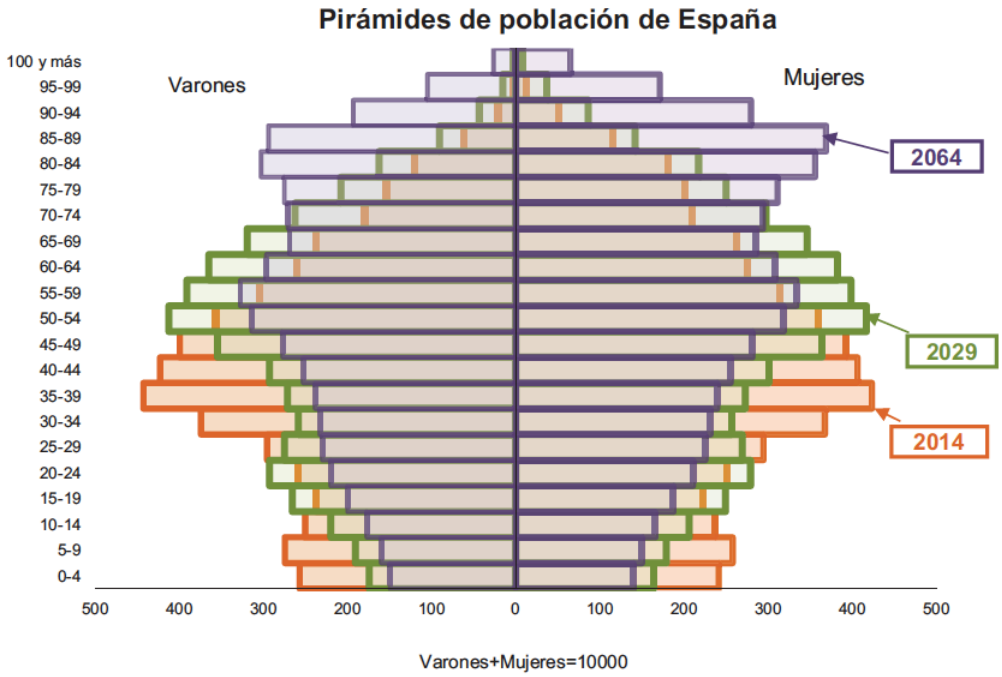

***Figura 2**: Pirámide de población de España en 2014 y estimaciones para los años 2029 y 2064 según datos del Instituto Nacional de Estadística.*

En los países en vías de desarrollo también es previsible un aumento de la incidencia aunque por diferente motivo. En estos países la natalidad es mucho más elevada, esto hace que se diluya el efecto del envejecimiento de la población y sea menos marcado que en los países desarrollados. Sin embargo, es el aumento en el consumo de tabaco, y la mayor exposición a agentes cancerígenos en entornos laborales con legislación más laxa, lo que hace que el tumor vesical sea una patología con incidencia creciente[3].

Ha sido ampliamente descrita la variabilidad de la incidencia en función de la zona geográfica, observándose las tasas más altas en áreas desarrolladas. A nivel mundial la tasa de incidencia ajustada por edad es de 10,1 casos nuevos por 100000 habitantes para los hombres y 2,5 para las mujeres. En la Unión Europea, estas cifras aumentan a 19,1 casos nuevos por 100000 habitantes para los hombres y 4,0 para las mujeres. Dentro

del marco europeo, según registros actuales, nuestro país presenta una de las incidencias más altas de su entorno, ocupando el tercer puesto por detrás de Bélgica y Malta, siendo nuestra tasa de incidencia ajustada por edad de 20,08 casos por 100000 habitantes [6,7]. A día de hoy no existe una explicación clara que justifique el porqué de esta incidencia tan elevada. No se han descrito diferencias entre la población de nuestro país y el resto de países europeos, aunque sí una mayor incidencia de población fumadora[8].

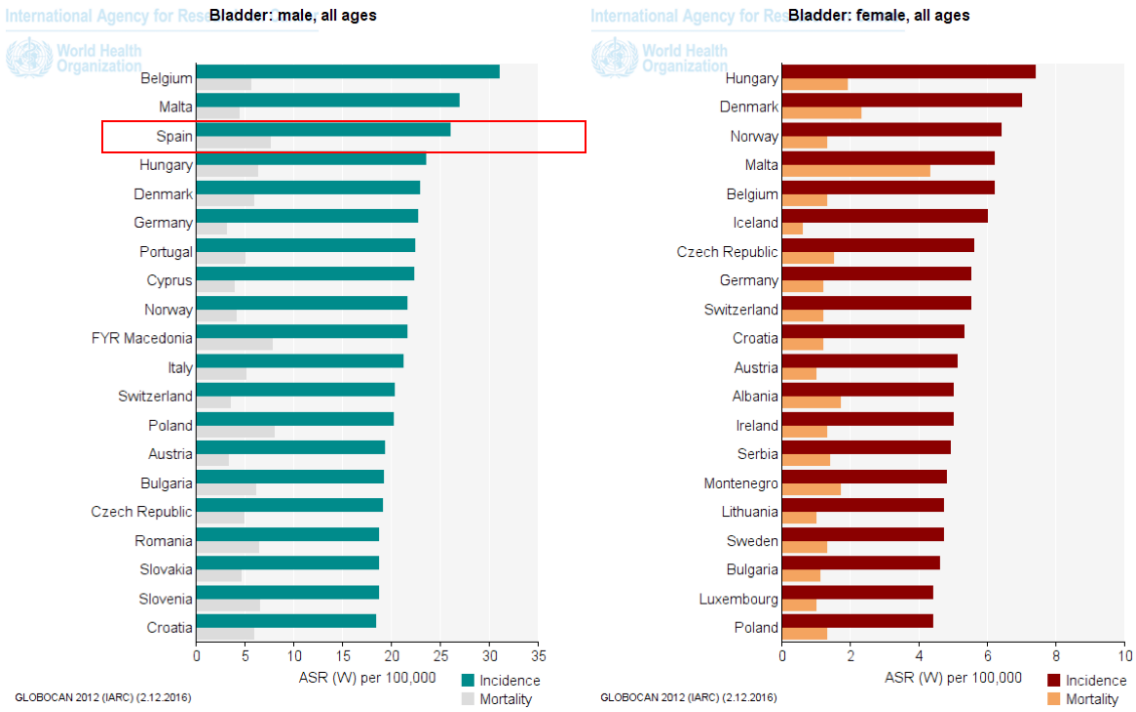

***Figura 3**: Incidencia y mortalidad del cáncer vesical en los países de la Unión Europea para varones (izquierda) y mujeres (derecha) de todas las edades*[1].

Durante el año 2011, la Asociación Española de Urología realizó un registro hospitalario de ámbito nacional sobre cáncer vesical. El objetivo de este estudio fue determinar la incidencia real del cáncer vesical en España y las características clínicas de los pacientes, así como evaluar el manejo clínico-terapéutico realizado. Según los

resultados de este estudio, la incidencia en nuestro país es de 24 nuevos casos por 100.000 habitantes/año, con un ratio en los diagnósticos hombre:mujer de 5:1, también alto dentro del marco europeo [7].

Cabe destacar que la incidencia por sexos en nuestro país está variando en los últimos años con unas tendencias totalmente opuestas. Esto puede explicarse por las diferencias en el consumo de tabaco entre hombres y mujeres, ya que tanto en Europa como en nuestro país, el consumo en el varón se inicia con unos 20 años de antelación con respecto a la mujer, y así mismo, el abandono del hábito tabáquico y la disminución en la prevalencia de fumadores sigue el mismo patrón con el mismo decalaje temporal entre hombres y mujeres. Como consecuencia, la incidencia de tumor vesical en el varón en nuestro país está disminuyendo de forma progresiva, mientras que en las mujeres todavía se espera un incremento progresivo importante de la prevalencia, la incidencia y la mortalidad hasta el año 2022 [9].

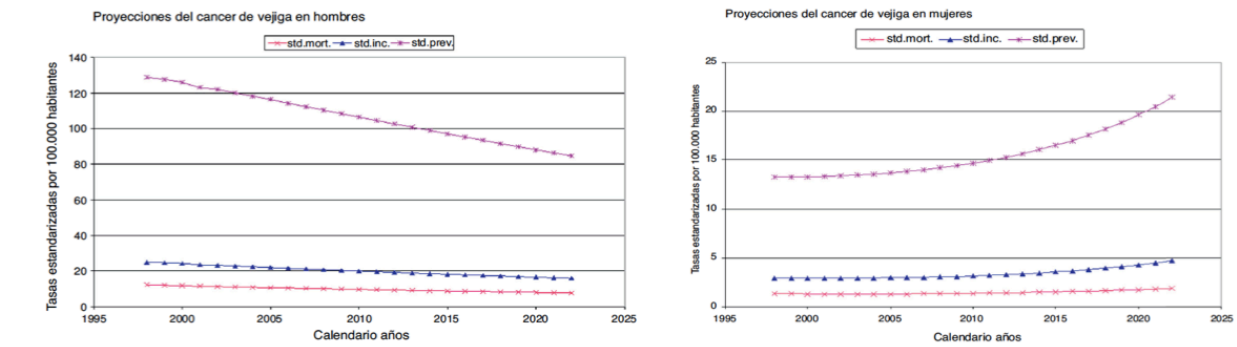

Figura 4*:Proyecciones del cáncer de vejiga en hombres (izquierda) y mujeres (derecha) 1998-2022*[9].

1.2. Estadificación del cáncer de vejiga

Aunque existen varios subtipos histológicos de cáncer vesical, aproximadamente el 90% de los tumores de nuevo diagnóstico son carcinomas de células transicionales. El sistema de estadificación usado en la actualidad (American Joint Commitee on Cancer tumor-node-metastatis: AJCC-TNM) permite la descripción de la afectación tumoral a nivel local, de los ganglios linfáticos loco-regionales, así como de la presencia o no de metástasis a distancia[10].

T Tumor primario
Tx: No se puede evaluar el tumor primario
T0: Ausencia de tumor
Ta: Tumor papilar que afecta a la mucosa
Tis: Carcinoma *in situ,* lesión plana
T1: Tumor que invade la lámina propia
T2: Tumor músculo-invasivo
T2a: Tumor que infiltra la capa muscular superficial (mitad interna)
T2b: Tumor que infiltra la capa muscular profunda (mitad externa)
T3: Tumor que invade el tejido perivesical
T3a: Microscópicamente
T3b: Macroscópicamente (masa extravesical)
T4: El tumor invade cualquiera de las estructuras siguientes: próstata, útero, vagina, pared de la pelvis, pared abdominal
T4a: El tumor invade la próstata (invasión estromal), el útero o la vagina
T4b: El tumor invade la pared de la pelvis o la pared abdominal
N Ganglios linfáticos
Nx: No se puede evaluar los ganglios linfáticos
N0: Ausencia de metástasis en ganglios linfáticos
N1: Metástasis en un ganglio linfático de la pelvis verdadera (hipogástrico, obturador, ilíaco externo, presacro)
N2: Metástasis múltiples (> 1 ganglio) en pelvis verdadera (hipogástrico, obturador, ilíaco externo, presacro)
N3: Metástasis en ganglios de la cadena ilíaca primitiva
M Metástasis a distancia
Mx: No se puede evaluar las metástasis a distancia
M0: Ausencia de metástasis a distancia
M1: Metástasis a distancia

Tabla 1: *Estadificación del cáncer vesical (AJCC-TNM Edición 7).*

La séptima edición de la clasificación AJCC-TNM fue publicada en 2009 y es la que se sigue empleando en la actualidad. Esta edición incluye algunas modificaciones con respecto a la clasificación anterior publicada en 2002[11]. Por un lado tumores que presentan invasión subepitelial de la uretra prostática ya no son considerados un estadio T4 y sólo se incluyen en este estadio aquellos tumores en los que la invasión es estromal. Por otro lado, la evaluación ganglionar en la clasificación actual se basa en la localización de los ganglios afectados mientras que en la clasificación antigua esto se hacía en función del tamaño de los mismos.

1.3. Historia natural del tumor vesical no músculo-invasivo

Aproximadamente el 75% de los pacientes afectos de esta patología presentan tumores vesicales no músculo-invasivos, es decir, que afectan sólo a la mucosa (estadio Ta o carcinoma in situ (CIS)) o bien a mucosa y submucosa (estadio T1) [10].

El curso natural de la enfermedad en el caso de los tumores no músculo-invasivos, hace que de forma global se comporten como una enfermedad muy recidivante a nivel vesical, pero con una tasa de progresión baja. Esto les convierte en tumores con una supervivencia bastante elevada, en comparación a los tumores con invasión de la capa muscular (estadios T2-T4)[12]. Al ser una patología muy recidivante con una supervivencia alta, los pacientes han de ser sometidos a seguimientos muy largos, y en ocasiones a múltiples intervenciones a lo largo de su vida.

La historia natural de estos tumores varía en función de determinados factores biológicos, clínicos y anatomopatológicos, por lo que es importante conocer cuáles son los factores de riesgo más importantes de recidiva y progresión para estimar de forma

individualizada el curso de la enfermedad esperable en cada caso y ajustar el tratamiento y el seguimiento según estos factores.

Un aspecto también a tener en cuenta es que estos seguimientos tan prolongados y las múltiples pruebas diagnósticas o intervenciones que precisan estos pacientes trae consigo un alto coste sanitario. El tumor vesical es la patología oncológica con los costes por paciente más elevados calculados a lo largo de la vida de los enfermos[13]. En el momento actual, donde la medición del gasto ha cobrado una gran relevancia, es importante determinar el impacto que supone esta enfermedad en los distintos sistemas sanitarios y buscar estrategias de tratamiento y seguimiento optimizadas de forma individual.

1.4. Factores pronósticos de recidiva y progresión

La individualización del pronóstico en la enfermedad oncológica vendrá en un futuro inexorablemente ligado a la evaluación de factores genéticos que determinen de forma individual la mejor estrategia terapéutica en cada caso. En este sentido en el tumor vesical, uno de los descubrimientos más importantes conseguidos en los últimos años ha sido el proyecto "The Cancer Genome Atlas (TCGA)" que ha permitido el análisis del mapa del genoma del cáncer de vejiga[14]. Las líneas de investigación basadas en el análisis del genoma abren nuevas expectativas en cuanto a la personalización de los tratamientos. Se busca conocer qué factores genéticos son los que determinan qué tumores responderán o no a un tratamiento y establecer terapias que se ajusten a las características de cada neoplasia y cada paciente. Sin embargo, la repercusión de estos avances en la atención médica diaria aún es muy limitada.

A día de hoy, la práctica clínica sigue basándose en factores clínicos y

anatomopatológicos que intentan determinar el riesgo de recidiva y progresión de estos tumores, así como el pronóstico de la enfermedad en cada caso. El estadio tumoral supone uno de los factores pronósticos más importantes descritos y junto con el grado de diferenciación de las células tumorales van a marcar el curso de la enfermedad. Otros factores pronósticos descritos son la multifocalidad, el tamaño tumoral, la presencia de CIS asociado, la tasa de recidiva previa o los tratamientos adyuvantes recibidos[15–17].

La importancia pronóstica de las distintas variables clínicas descritas varía mucho de unos estudios a otros. Sin embargo, en el año 2006 la EORTC (European Organisation for Research and Treatment of Cancer) publica unas tablas para el cálculo de riesgo de recidiva y progresión tumoral en los pacientes con tumor vesical no músculo-invasivo, en las que utiliza y pondera los seis factores pronósticos clínicos y patológicos más importantes:

- Estadio
- Grado
- Número de tumores
- Tamaño tumoral
- Presencia de CIS asociado
- Tasa de recidiva previa

A cada uno de estos factores se les asigna una puntuación y el sumatorio de estas puntuaciones es el que establece el riesgo de recidiva y progresión a uno y cinco años de cada paciente.

FACTOR	RECIDIVA	PROGRESION
Número de tumores		
Tumor único	0	0
2-7	3	3
≥ 8	6	3
Tamaño tumoral		
< 3cm	0	0
≥ 3	3	3
Tasa de recidiva previa		
Tumor primario	0	0
≤ 1 recidiva/año	2	2
> 1 recidiva/año	4	2
Estadio		
Ta	0	0
T1	1	4
CIS asociado		
No	0	0
Si	1	6
Grado		
G1	0	0
G2	1	0
G3	2	5
PUNTUACION TOTAL	**0-17**	**0-23**

***Figura 5**: Tablas de la EORTC para el cálculo de riesgo de recidiva y progresión en pacientes con tumor vesical no músculo-invasivo*[18].

Puntuación recidiva	Probabilidad de recidiva a 1 año		Probabilidad de recidiva a 5 años	
	%	(IC 95%)	%	(IC 95%)
0	15	(10-19)	31	(24-37)
1-4	24	(21-26)	46	(42-49)
5-9	38	(35-41)	62	(58-65)
10-17	61	(55-67)	78	(73-84)

Puntuación progresión	Probabilidad de progresión a 1 año		Probabilidad de progresión a 5 años	
	%	(IC 95%)		%
0	0,2	(0-0,7)	0	0,2
2-6	1	(0,4-1,6)	2-6	1
7-13	5	(4-7)	7-13	5
14-23	17	(10-24)	14-23	17

***Figura 6**: Probabilidad de recidiva y progresión de acuerdo a la puntuación total obtenida*[18].

Esta publicación puso al alcance de la comunidad urológica una herramienta informática sencilla para clasificar a los pacientes en grupos de riesgo según las características tumorales[18], hecho muy importante a la hora de estandarizar el seguimiento y el tratamiento de los enfermos.

Así, basado en los factores pronósticos disponibles, y en particular en los datos de la EORTC, se han establecido tres grupos de riesgo (Tabla 2).

Tumores de bajo riesgo
• Tumor primario • Tumor único • Estadio Ta • Grado G1 (Bajo grado según la clasificación de la OMS 2004) • Tumor menor de 3cm • No asociación de CIS
Tumores de riesgo intermedio
Aquellos tumores que no se incluyen dentro de las características de bajo riesgo ni de alto riesgo
Tumores de alto riesgo
Aquellos tumores que presenten cualquiera de estas características: • Estadio T1 • Grado G3 (Alto grado según la clasificación de la OMS 2004) • Asociación CIS • Tumor múltiple, recidivante, con tamaño mayor de 3cm, estadio Ta y grado G1-G2 (cumpliendo todas estas características)

Tabla 2: *Grupos de riesgo de tumor vesical.*

La clasificación de los pacientes en función del riesgo individual determina la toma de decisiones clínicas diarias en cuanto a la necesidad de tratamientos adyuvantes, la elección de los mismos y el seguimiento óptimo en cada caso.

1.5. Tratamiento del tumor vesical no músculo-invasivo

La resección transuretral en el tumor vesical es el tratamiento inicial de elección en todos los casos. Mediante esta técnica se consigue no sólo realizar una correcta estadificación tumoral, sino la erradicación completa del tumor en casos de tumores papilares Ta-T1. Debido a la historia natural de este tumor, y a la alta tasa de recidiva referida anteriormente es necesario considerar la necesidad de tratamientos adyuvantes.

La instilación intravesical postoperatoria de agentes quimioterápicos como la mitomicina C ha demostrado ser efectiva para disminuir la tasa recidiva tumoral [19].

En los tumores de bajo riesgo, la instilación única postoperatoria puede considerarse suficiente como tratamiento adyuvante. En tumores de riesgo intermedio o alto riesgo, este tratamiento es considerado subóptimo, por lo que es preciso valorar la necesidad de otros tratamientos adyuvantes como son los ciclos de instilaciones de quimioterpia intravesical o bien las instilaciones de inmunoterapia intravesical con el bacilo de Calmette-Guérin (BCG) [20].

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JUSTIFICACIÓN e HIPÓTESIS

2. JUSTIFICACIÓN e HIPÓTESIS

Todo lo referido anteriormente ha motivado la investigación y el desarrollo de tres líneas de trabajo que se exponen en esta tesis y que han dado lugar a cuatro publicaciones en el ámbito internacional.

***Validación externa de las tablas de riesgo de la EORTC*.**

La publicación de las tablas de la EORTC supuso la difusión del modelo pronóstico más empleado en el tumor vesical no músculo-invasivo. Para la elaboración de estas tablas se utilizaron los datos de pacientes incluidos en 7 ensayos clínicos que analizaban el efecto de distintos tipos de quimioterapia intravesical postoperatoria sobre la recidiva y la progresión de la enfermedad. Ninguno de estos ensayos fue realizado con población española, lo que nos plantea como primera hipótesis que es posible que los pacientes de nuestro país no sean, por algún motivo, comparables a los que fueron incluidos en dichos estudios, y por tanto estas tablas no serían aplicables en nuestro medio.

Además, a pesar de que los ensayos clínicos suponen la mayor evidencia científica de la que disponemos en la práctica médica, ya que aportan una alta potencia estadística para probar el efecto del factor de estudio, en ocasiones, sus resultados no son aplicables ni extrapolables a la práctica clínica diaria, debido la excesiva selección de los pacientes, lo que impide reproducibilidad de sus conclusiones posteriormente en la práctica médica.

Por estos motivos se consideró necesario realizar una validación externa de las tablas de riesgo de la EORTC y determinar la aplicabilidad de estas predicciones en los pacientes de nuestro medio.

Para ello, la primera parte de nuestro trabajo se basó principalmente en la elaboración de la base de datos institucional de cáncer de vejiga, el mantenimiento actualizado prospectivamente de la misma y el análisis posterior de los resultados, paso elemental sin el cual es imposible conocer con exactitud los resultados individuales y hacer una comparación crítica con los resultados publicados por otros grupos. Se calculó el riesgo de recidiva y progresión a un año y cinco años de los pacientes con tumor vesical no músculo-invasivo intervenidos en nuestro centro, utilizando la misma metodología seguida en el estudio de referencia con el fin de realizar una validación externa y determinar la aplicabilidad de estas tablas en los pacientes de nuestro medio.

Virginia Hernández, E. De La Peña, M.D. Martín, et al. External validation and applicability of the EORTC risk tables for non-muscle invasive bladder cancer. World J Urol. 2011 Aug;29(4):409-14. (Q2. FI 2,411).

Búsqueda de nuevos factores predictivos

Como se comentó anteriormente, España es un país con una incidencia de tumor vesical superior a la de los países de su entorno. Se desconoce qué factores epidemiológicos pueden ser diferentes y justificar estar diferencias. Es por esto que a falta aún de factores pronósticos basados en la genómica o la proteómica, es necesario establecer nuevos factores predictivos que nos ayuden a guiar las mejores estrategias terapéuticas para nuestros pacientes, de la forma más individualizada posible.

Uno de los factores pronósticos más estudiado y utilizado en el tumor vesical no músculo-invasivo ha sido el tamaño tumoral. Actualmente un tamaño tumoral mayor

de 3 centímetros es considerado de mal pronóstico y es una de las variables que se ha de tener en cuenta al utilizar la calculadora de recidiva y progresión basada en las tablas publicadas por la EORTC. En concreto el valor ponderado que adquiere el tamaño tumoral en estas tablas para la recidiva (no así para la progresión tumoral) es superior al estadio patológico T y el grado de diferenciación G.

El tamaño, sin embargo, es una variable imprecisa. De todas las variables incluidas en las tablas de riesgo, ésta es la más inexacta puesto que la medición del tamaño no se realiza de manera objetiva y reproducible, sino que es práctica generalizada estimar el tamaño de forma visual. Además, existen situaciones clínicas en las que la determinación del tamaño tumoral resulta dudosa: enfermedad múltiple de pequeño tamaño, tumores satélites muy próximos al tumor principal, o por ejemplo, tumores de base de implantación estrecha pero muy voluminosos.

Por este motivo se consideró interesante analizar una variable más objetiva, como es el peso en gramos de la muestra resecada en la resección transuretral como un nuevo factor pronóstico de recidiva y progresión sistemático, reproducible y objetivo.

E. De La Peña, Virginia Hernández, C. Blázquez, et al. Weight of the resected specimen after transurethral resection as a new predictive variable for recurrence of non-muscle-invasive bladder tumour. BJU Int. 2013 Apr;111(4 Pt B):E196-201(Q1. FI 3,046)

Individualización del tratamiento

Por último, conocer la biología tumoral es esencial para predecir su comportamiento e individualizar las estrategias de tratamiento. Con los factores pronósticos de los que disponemos hasta el momento clasificamos a los pacientes en grupos de riesgo y esto determina decisiones muy importantes en la práctica clínica diaria cómo cuál es el mejor esquema de seguimiento, qué tratamiento adyuvante es preciso en cada caso, o incluso si es recomendable o no optar por tratamientos más radicales como la cistectomía.

La resección transuretral sigue siendo la opción terapéutica de elección tanto al diagnóstico, como en el tratamiento de las recidivas. Los pacientes con tumores vesicales no músculo-invasivos son sometidos, en numerosas ocasiones, a este procedimiento a lo largo del seguimiento, no sin presentar desafortunadamente complicaciones y efectos secundarios que, en ocasiones, pueden ser severos. Esta cirugía se practica en algunas ocasiones para erradicar recidivas tumorales de mínimo tamaño en las que la experiencia diaria nos pone de manifiesto su indolencia. En estos casos la cirugía podría considerarse un sobretratamiento y es por esto que, en nuestro centro, desde el año 1999 se está sometiendo a observación vigilada a un grupo de pacientes con recidivas de tumores vesicales que por su historia clínica y por sus características tumorales invitan a suponer que son indolentes, y por lo tanto, en este grupo de enfermos se podría demorar la cirugía con el fin de disminuir el número de intervenciones a las que sometemos a estos pacientes a lo largo de su vida. Sin embargo, al inicio de este programa existía controversia en cuanto la seguridad del mismo a largo plazo, el riesgo de progresión tumoral tanto en grado como en estadio y la aceptación por parte de los pacientes. Es por ello que se consideró relevante analizar la seguridad

oncológica de este programa de vigilancia activa, en un grupo de pacientes muy seleccionado, con recidivas vesicales que por su tamaño, aspecto cistoscópico y anatomía patológica anterior, fueron considerados de muy bajo riesgo.

Virginia Hernández, M. Álvarez, E. De la Peña, et al. Safety of an active surveillance program for recurrent non-muscle-invasive bladder carcinoma. Urology. 2009 Jun;73(6):1306-10. (Q2. FI 2,365)

Este estudio inicial fue evaluado con un periodo de seguimiento más amplio, concretando aún más la selección de pacientes candidatos a ser incluidos en él, fruto de la experiencia sedimentada del equipo investigador, el aumento del número de pacientes reclutados y la discusión de nuestros resultados en diversos foros internacionales.

Virginia Hernández, C. Llorente, E. de la Peña, et al. Long-term oncological outcomes of an active surveillance program in recurrent low grade ta bladder cancer. Urol Oncol. 2016 Apr;34(4):165.e19-23. (Q1. FI 2,921)

OBJETIVOS

OBJETIVOS

1. Validación externa de las tablas de riesgo de la EORTC, que es actualmente la herramienta más importante de la que se dispone para la estimación del riesgo de recidiva y progresión, a uno y cinco años, de pacientes con tumor vesical no músculo-invasivo. Este trabajo supone la primera validación externa realizada de dichas tablas en la práctica clínica.

2. La búsqueda de nuevos factores de recidiva y progresión, en concreto el análisis del peso tumoral de la muestra resecada en gramos como un nuevo factor pronóstico reproducible y objetivo, no descrito hasta el momento.

3. Por último, determinar la seguridad oncológica de una nueva estrategia de tratamiento como es la vigilancia activa en tumores que por sus características clínico-patológicas pueden ser considerados como de muy bajo riesgo. Hasta la fecha este programa goza de la mayor casuística mundial y el periodo de seguimiento más largo publicado.

MATERIAL y MÉTODOS, RESULTADOS, DISCUSIÓN

La presente tesis doctoral está realizada mediante compendio de artículos científicos. Por este motivo cada uno de los apartados de Material y Métodos, Resultados y Discusión se desarrollan por separado en cada una de las siguientes publicaciones:

Publicación 1:

Virginia Hernández, E. De La Peña, M.D. Martín, et al. External validation and applicability of the EORTC risk tables for non-muscle invasive bladder cancer. World J Urol. 2011 Aug;29(4):409-14. (Q2. FI 2,411).

Publicación 2:

E. De La Peña, Virginia Hernández, C. Blázquez, et al. Weight of the resected specimen after transurethral resection as a new predictive variable for recurrence of non-muscle-invasive bladder tumour. BJU Int. 2013 Apr;111(4 Pt B):E196-201(Q1. FI 3,046)

Publicación 3:

Virginia Hernández, M. Álvarez, E. De la Peña, et al. Safety of an active surveillance program for recurrent non-muscle-invasive bladder carcinoma. Urology. 2009 Jun;73(6):1306-10. (Q2. FI 2,365)

Publicación 4:

Virginia Hernández, C. Llorente, E. de la Peña, et al. Long-term oncological outcomes of an active surveillance program in recurrent low grade ta bladder cancer. Urol Oncol. 2016 Apr;34(4):165.e19-23. (Q1. FI 2,921)

EXTERNAL VALIDATION AND APPLICABILITY OF THE EORTC RISK TABLES FOR NON-MUSCLE-INVASIVE BLADDER CANCER.

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World J Urol. 2011 Aug;29(4):409-14.

Q2. FI 2,411

ABSTRACT

Objectives: To perform an external validation of the EORTC risk tables and to evaluate their applicability in the patients of our institution by comparing the actual risk of recurrence and progression in our series to those obtained through the application of the EORTC tables.

Materials and Methods: Retrospective study, based on a prospective cohort of 417 patients in follow-up with primary TaT1 bladder tumours, operated on in our centre between 1998 and 2008 and collected in our database. Risk scores were assigned depending on the tumour characteristics to divide our series into four risk groups according to these ratings. An analysis of survival was carried out to calculate the probability of recurrence by the method of Kaplan-Meier.

Results: A total of 417 patients with a median follow-up of 59 months were studied. The overall recurrence and progression rates of our series were 25.95% (21.97-30.49) and 4.86% (3.16-7.43) at 1 year, and 53.46% (48.06-59.05) and 8.43% (5.95-11.86) at 5 years, respectively. When we compare our rates of recurrence and progression by groups with the corresponding values from Sylvester's publication, an overlapping of the confidence intervals between both populations is detected.

Conclusions: In terms of the applicability of the EORTC risk-tables in our patients' population, we conclude that these tables predict accurately the clinical course of patients with NMIBC. Due to the sample size of our study, we can only validate the recurrence model of the EORTC tables.

INTRODUCTION

Since its publication in 2006 by Sylvester et al.[1], a useful risk calculator is available that allows a straightforward categorization of patients with non-muscle invasive bladder cancer (NMIBC). EORTC tables provide us with the 1- and 5-year risk of recurrence and progression, enabling us to make a decision regarding the need and type of adjuvant therapy. This risk categorization brings patients homogenization for their inclusion in clinical trials and allows for comparison and a better potential for future meta-analysis and treatment efficacy comparison.

Patient data from seven different clinical trials in European countries other than ours were used in the elaboration of the EORTC tables. Spain is a country with a high incidence of bladder cancer and thus, it might be the case that these tables are not applicable in our setting. In addition, no external validation study has been performed to date, so, following the recommendations of the authors we intend to calculate the 1- and 5-year risk of recurrence and progression of those patients operated on in our institution and then compare our results with those predicted by the EORTC risk tables.

MATERIALS AND METHODS

Our study is retrospective, based on a prospective cohort of patients collected in our database NMIBC, operated on in our institution between 1998 and 2008, classified according to the 2002 TNM classification. Those patients operated on before 2002 were retrospectively classified. One single immediate, post-operative intravesical instillation of chemotherapy with MMC was administered in all cases whenever (1) gross active hematuria was absent, (2) the ureteral orifice had not been resected, or (3) a well-founded suspicion of bladder perforation was not observed by the operating urologist. In short, highly recurrent, intermediate-risk patients were offered a 6-week course of MMC and high-risk patients were offered BCG induction plus maintenance if a response was obtained.

A review of all clinical trials included in the analysis[2–7] that set the basis for the elaboration of the EORTC tables has been made to asses how our patients compare with those of the initial trials. We have used the same methodology as that described by Sylvester[1] giving our patients the same risk score after which they were grouped into four risk categories. Progression is defined as conversion to muscle-invasive status at any time in the follow-up.

For univariate analysis, the X^2 test was used to assess the association between categoric variables. The Kaplan-Meier method was used to estimate the risks of recurrence and progression. Recurrence and progression curves were estimated by the Kaplan-Meier method and differences between curves were evaluated with the log-rank test. Multivariate Cox models were used to compare the predictive performance for recurrence and progression. The proportional hazards assumption was tested by

introducing variables into the model created by multiplying each variable by time. Multivariate Cox analysis was also used to evaluate recurrence and progression.

Patients known to have died from causes unrelated to bladder cancer were censored in the recurrence and progression analysis; p values of 0.05 or less were considered statistically significant. The SPSS 15.0 and STATA 10.0 software programs were used for these analyses. To assess model accuracy (discrimination) at one and 5 years, receiver operating characteristic (ROC) curves were calculated. This study was approved by the ethics committee of our institution.

RESULTS

We have studied 417 new patients with an initial first diagnosis of non-muscle-invasive transitional cell carcinoma and who were monitored during a median time of 59 months. Mean age of our study population was 68.8 years and 83.5% of them were men. The main characteristics of the patients are shown in Table 1. The rate of total loss from follow-up was 4.1% (17 patients), in 3 patients, it was due to death non-related to bladder cancer.

Variables	N (%)
Number of tumours	
Single	283 (70.8%)
2-7 tumours	115 (28.8%)
>7 tumours	2(0.5%)
Tumour size	
<3cm	223 (59.8%)
≥3cm	150 (40.2%)
Recurrence rate	
Non-recurrent	219 (52.5%)
<1 recurrence/year	167 (40%)
>1 recurrence/year	31 (7.4%)
T category	
Ta	227 (58.1%)
T1	164 (41.9%)
Grade	
G1	220 (54.7%)
G2	142(35.3%)
G3	40 (10%)
CIS	
Yes	14 (3.4%)
No	403 (96.6%)
Intravesical treatment	
MMC single dose	274 (70,3%)
BCG	8.2% (30)
MMC course	3.3% (14)

Table 1. *Description of the series*

Our series was fully comparable in every variable, except for two, with those of the clinical trials reviewed. Regarding the number of tumours, we had 70% single tumours compared with 56% in the overall series and, likewise, differences in the tumour size were noted with 20% more tumours <3 cm in our series than in the global series. However, this difference was not so noticeable when our series was individually compared with individual series of each clinical trial as it is the series of Bouffioux where 61% of patients had single tumours in one group or Witjes et al. [6] where the percentage of patients with tumours <3cm was 67% compared with 59 % in our series ($p = 0.06$).

Univariate analysis shows that the number of tumours, grade and recurrence rate are associated with a higher risk of recurrence. Similarly, sex, size, stage, grade and adjuvant therapy are the variables statistically associated with the risk of progression (Table 2).

Variables	Recurrence		Progression	
	HR (CI 95%)	p	HR (CI 95%)	p
Gender				
Male, female	1.01 (0.69-1.47)	0.95	2.4 (1.2-5)	0.01
Age				
≤ 65 years, > 65 years	1.01 (0.65-1.35)	0.94	0.83 (0.40-1.67)	0.06
Number tumours				
Single, multiple	1.93 (1.44-2.59)	<0.001	1.57 (0.78-3.2)	0.20
Size				
< 3cm, ≥ 3 cm	1.33 (0.96-1.8)	0.06	1.97 (0.93-4.16)	0.07
Recurrence rate				
≤ 1rec/year, > 1rec/year	1.5 (1.4-2.3)	0.03	0.90 (0.31-2.6)	0.85
T category				
Ta, T1	1.31 (0.98-1.7)	0.06	3.06 (1.44-6.52)	0.004
Grade: G1, G2, G3				
G2	1.55 (1.14-2.1)	0.005	5.8 (2.15-15.62)	0.001
G3	1.98 (1.2-3.2)	0.006	10.6 (3.34-33.7)	<0.0001
T1G3				
No, yes	1.5 (0.9-2.5)	0.11	4.24 (1.8-9.8)	0.001
CIS				
No, yes	0.69 (0.28-1.68)	0.42	1.96 (1.3-7.0)	0.97
Intravesical treatment				
No,yes	0.97 (0.6-1.6)	0.92	0.42 (0.17-1.0)	0.05

Table 2. *Univariate analysis of recurrence and progression*

Multivariate analysis identified size, stage, grade and the recurrence rate as the prognostic variables associated with the risk of recurrence. The number of tumours was not an independent predictor in the logistic regression model. The variables that proved to predict the risk of progression were recurrence, stage and grade (Table 3). For this model the area under the curve was 0.75 for recurrence (0.61 at 1-year recurrence and 0.70 at 5-year recurrence) and 0.54 for progression (0.58 at 1-year progression and 0.55 at five-year progression).

Variables	Recurrence		Progression	
	HR (CI 95%)	p	HR (CI 95%)	p
Number tumours				
Single, multiple	1.24 (0.89-1.71)	0.19	-	
Size				
< 3cm, ≥ 3 cm	1.86 (1.33-2.58)	<0.0001	-	
Recurrence rate:				
≤ 1rec/year, > 1rec/year	8.38 (6.50-10.8)	<0.0001	-	
T category				
Ta, T1	1.41 (0.98-2,01)	0.05	2.35 (1.05-5.2)	0.03
Grade				
G3	4.21 (2.2-7.7)	<0.0001	2.61 (1.06-6.41)	0.03
Recurrence				
Yes,no	-		3.18 (1.36-7.42)	0.007

***Table 3**. Multivariate analysis of risk of recurrence and progression*

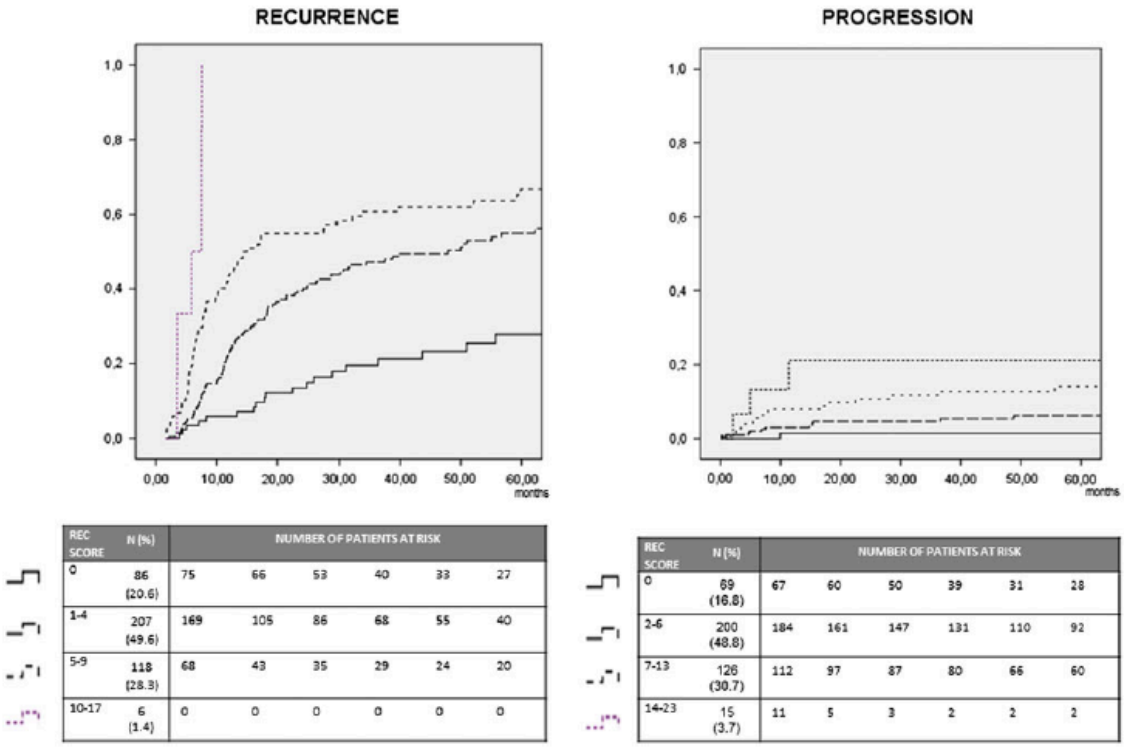
One hundred and ninety-eight patients (47.5%) recurred during the follow-up, and 34 (8.2%) progressed in stage. The overall recurrence and progression rates of our series were 25.95% (21.97-30.49) and 4.86% (3.16-7.43) at 1 year, and 53.46% (48.06-59.05) and 8.43% (5.95-11.86) at 5 years, respectively.

Table 4 shows the risks of recurrence and progression according to the weighted variables compared with those of the work by Sylvester et al. Kaplan-Meier survival curves of recurrence and progression are shown in Figure 1. An overlapping of the confidence intervals between both populations is detected.

	Present Series		
Rec Score	**N (%)**	**Prob recurrence 1year (CI 95%)**	**Prob recurrence 5years (CI 95%)**
0	86 (20.6)	5.9%(2.5%-13.6%)	27.9% (18.4%-40.9%)
1-4	207 (49.6)	22.4%(17.2%-28.9%)	54.9% (47.3%-63.0%)
5-9	118 (28.3)	42.8%(34.4%-52.3%)	66.84% (57.2%-76.2%)
10-17	6 (1.4)	50.0%(19.6%-88.9%)	50.0% (19.6%-88.9%)
Prog Score	**N (%)**	**Prob progression 1year (CI 95%)**	**Prob progression 5years (CI 95%)**
0	69 (16.8)	1.4% (0.2%-9.8%)	1.4% (0.2%-9.8%)
2-6	200 (48.8)	3.0% (1.4%-6.6%)	6.2% (3.5%-11.1%)
7-13	126 (30.7)	7.9% (4.4%-14.3%)	14.1 % (8.8%-22.2%)
14-23	15 (3.7)	21.2% (7.3%-52.%)	21.2% (7.3%-52.7%)

	Sylvester series		
Rec Score	**N (%)**	**Prob recurrence 1year (CI 95%)**	**Prob recurrence 5years (CI 95%)**
0	271(10.4)	15%(10%-19%)	31% (24%-37%)
1-4	1022 (39.3)	24%(21%-26%)	46% (42%-49%)
5-9	944 (36.3)	38%(35%-41%)	62% (58%-65%)
10-17	259 (9.97)	61%(55%-67%)	78% (73%-84%)
Prog Score	**N (%)**	**Prob progression 1year (CI 95%)**	**Prob progression 5years (CI 95%)**
0	431 (16.6)	0.2%(0%-7%)	0.8% (0%-1.7%)
2-6	1238 (47.7)	1.0%(0,4%-1,6%)	6% (5%-8%)
7-13	712 (27.4)	5%(4%-7%)	17 % (14%-20%)
14-23	119 (4.6)	17%(10%-24%)	45% (35%-55%)

***Table 4**. Risks of recurrence and progression at one year and five years in groups based on the weighted variables*



REC SCORE	N (%)	NUMBER OF PATIENTS AT RISK					
0	86 (20.6)	75	66	53	40	33	27
1-4	207 (49.6)	169	105	86	68	55	40
5-9	118 (28.3)	68	43	35	29	24	20
10-17	6 (1.4)	0	0	0	0	0	0

REC SCORE	N (%)	NUMBER OF PATIENTS AT RISK					
0	69 (16.8)	67	60	50	39	31	28
2-6	200 (48.8)	184	161	147	131	110	92
7-13	126 (30.7)	112	97	87	80	66	60
14-23	15 (3.7)	11	5	3	2	2	2

Fig 1. *Kaplan-Meier survival curves of recurrence and progression.*

DISCUSSION

Non-muscle invasive bladder tumours are a type of neoplastic disease that features a high recurrence rate and has the highest lifetime treatment costs per patient of all cancers [8]. An accurate estimation of the risks of recurrence and progression in the individual patient can help in the decision-making process regarding the most appropriate therapy such as bladder fulguration[9], adjuvant treatment [10] or even surveillance of some patients with low risk for recurrence and/or progression [11,12]. Intravesical bacillus Calmette-Guerin and intravesical chemotherapeutic agents are the therapies used currently for prevention of recurrence and progression[13]. There is now a need to develop new therapies to achieve this goal[14].

Bladder cancer is a highly prevalent disease. It is the 7th most common malignancy in men and 17th in women[15]. Incidence of bladder cancer is significantly higher in Spain than in other European countries with rates of 44,6/100,000 for male patient and 4,45/100,000 for female patient[16], with an overall age-adjusted mortality rate of 8.54, the highest of all European countries[17]. Some biological differences could be anticipated that precluded the use of the EORTC in our setting. At present, no population differences have been detected between the Spanish population and the rest of Europe, except for a higher incidence of smoking in our country [18].

The EORTC risk tables are the best currently existing prognostic model, and its use, as well as that of the guidelines of the European Association of Urology, should be the standard of care in our setting. The present study aims to validate the EORTC risk tables in our setting, which is the first external evaluation known. This assessment is always necessary to determine whether the nomograms, which are usually done with very large

series, are in addition to specific, applicable in lower volume centers, so that similar works have been published to validate invasive bladder cancer nomograms [19].

We first assessed the comparability of our series with that of the seven clinical trials used in the construction of the tables[2–7]. Our series differs in the number of single tumours with a higher value in our population. This difference could result in a lower risk of recurrence, and we speculate that this is the reason why our recurrence rate is as small as 5% but with a wide confidence interval (2.5-13.6%) due to the sample size. At 5 years time, however, both our overall rates and the confidence intervals are nearly equivalent. Due to this similarity, we hypothesize that the difference in the number of single tumours is not a confounding factor.

The variables associated with risk of recurrence and/or progression both in the univariate as in the multivariate analyses are those recognized as such in other studies: stage, grade and size[20]. Other variables proved to have a predictive value, as is the case of the number of tumours, which only showed a trend toward statistical significance that could improve its performance if we had had a larger sample size. Another limitation is the lack of precise surgical details that limit the analysis of databases.

The comparison of our rates of recurrence and progression with the values of the publication of Sylvester results in overlapping confidence intervals, which we interpret as a equivalence in those risk rates that allows us to believe that the EORTC risk table is a valid tool for our patient population.

To assess model accuracy (discrimination) at one and 5 years, Harrell's bias corrected concordance index was used in the original study. Their results in recurrence are very similar to our area under the curve (AUC). However, for progression, our results are not so accurate due to the low number of patients that have progressed in our cohort. Thus, our results can only validate the curves in terms of recurrence, not in terms of progression. Taking into account the Kaplan-Meier curves and confidence intervals, presumably, by increasing the sample size the results would have been more similar.

A predictive model for the calculation of the risk of recurrence and progression for patients treated with BCG has recently been published[21]. A limitation of our study is the size of the sample, especially in the high-risk group in which the number of patients is remarkably smaller. This makes it impossible to perform stratified analysis by type of intravesical treatment received and as the number of patients increases in this group, it will be necessary to review these results.

CONCLUSIONS

In terms of the applicability of the EORTC risk tables in our patients' population, we conclude that these tables predict accurately the clinical course of patients with non-muscle invasive bladder cancer. Due to the sample size of our study, we can only validate the recurrence model of the EORTC tables.

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WEIGHT OF THE RESECTED SPECIMEN AFTER TRANSURETHRAL RESECTION AS A NEW PREDICTIVE VARIABLE FOR RECURRENCE OF NON-MUSCLE-INVASIVE BLADDER TUMOUR.

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ABSTRACT

Objectives: To evaluate the role of the weight of the resected specimen after transurethral resection as a predictive factor of recurrence and progression of non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: The weight of the resected tumour was measured consecutively in 144 subjects who underwent transurethral resection of bladder tumours at our institution. The median (interquartile range[IQR]) follow-up was 58 (61.3) months.The probability of recurrence and progression at 1- and 5-years were calculated using the currently accepted variables. Thresholds for the specimen weight were determined according to percentiles and receiver-operating characteristics curves.

Results: The median (IQR) weight of the specimen was 6(16) g. Multivariate analysis showed that the weight of the resected specimen was an independent predictive risk factor for recurrence at a threshold value of 6g with a hazard ratio of 1.7 (95% confidence interval: 1.048-2.761) P = 0.03. Progression was not associated with the weight of the resected specimen

Conclusions: The weight of the resected specimen is a new variable for predicting the risk of recurrence of NMIBC. Tumours weighing > 6g, according to the present data, have a 1.7-fold higher likelihood of recurrence than those tumours that weigh less.

INTRODUCTION

The objective assessment of the recurrence and progression of non-muscle invasive bladder cancer (NMIBC) has been carried out by using a number of clinical and pathological tumour features [1]. These variables were given a score value and entered into a web-based calculator to help the clinician in the prediction of the clinical outcome [2]. The weighted score was based on six variables (number of tumours, tumour size, previous recurrence rate, T category, carcinoma in situ [CIS] and grade). The European Association of Urology subsequently adopted this system into its guidelines and, based on these scores [3], patients were stratified into low-, intermediate-and high-risk for recurrence[4]. This clinical tool has been validated in our practice[5] while other authors claim that underestimation of the results is the case in some subset of patients[6].

In addition, there is an ongoing debate on which predictive variables should be used for recurrence and progression of NMIBC. In a study by Fernández-Gomez et al.[6], multiplicity, previous tumour, female gender, and CIS were significant predictors of recurrence in multivariate analysis; however, according to other authors, grade and tumour stage were not predictive of recurrence and only tumour size and the use of intravesical instillations, in addition to the rest of those previously reported, were accurate predictors [1,7].

To evaluate size as a prognostic variable, Millán et al. defined tumour size as the largest tumour diameter measured with the resection loop that is ordinarily 1 cm long. Accordingly, size was categorized as <1.5 cm, 1.5-3 cm, and >3 cm. A threshold of 3 cm was set for the prognosis of NMIBC [1].

There are various clinical scenarios in which the measurement of tumour size is hampered by the tumour features, e.g. multiple small tumours and small tumours adjacent to a larger tumour. In addition, in many cases, tumour size does not represent the overall tumour burden, e.g. in solid tumours mixed with papillary lesions, or in bulky tumours with a small pedicle. Furthermore, endoscopic assessment of tumour size is highly subjective and not reproducible, being highly operator-dependent. With this in mind, we aimed to evaluate the role of the tumour specimen weight after transurethral resection of bladder tumour (TURBT) as a new and objectively measurable variable in the prediction of recurrence and progression of NMIBC.

MATERIALS AND METHODS

Patient population

From January 1999 to December 2009, 520 patients underwent TURBT in our institution for primary NMIBC. These patients' pathological and clinical data were prospectively entered into our bladder cancer database, and the transurethral resection (TUR) specimen of a subset of 144 consecutive patients was weighed.

Additional clinical data were entered in the database by an independent reviewer. The study was approved by our institutional review board and was conducted in accordance with the provisions of the Declaration of Helsinki. No additional tests were done to the patient apart from those included in routine standard clinical care.

Demographic variables were collected, as well as those included in the European Organisation for the Research and Treatment of Cancer (EORTC) risk tables by Sylvester et al.[2] in addition to the specimen weight. The study endpoints were recurrence and progression rates. The latter was defined as upstaging to muscle-invasive or metastatic disease. High-risk tumours Ta-T1 G3, with or without CIS were not excluded for study. Multiple random biopsies were not routinely performed. All re-TURs were excluded from the study. Histopathology results were classified according to the 2009 TNM system [8] and WHO (1973) grading system[9].

Technique and follow-up

Complete TURBT was always attempted and a biopsy of the deep muscle at the tumour base was obtained with the resection loop until healthy muscle or perivesical fat were seen. This base sample was submitted separately to the laboratory. Operations were

performed by eight urologists with > 10 years of experience or by residents supervised by these same urologists. Tumour size was defined as the largest dimension, as assessed by endoscopic viewing during resection. A second resection in high-risk tumours was considered when the initial resection was incomplete, when the tumour large or there were multiple tumours, or when the pathologist reported that the specimen contained no muscle tissue. Patients who were upgraded/upstaged (2.8%) were assigned to the most unfavourable category. One single immediate, postoperative intravesical instillation of chemotherapy with mitomycin C (MMC) was administered in all cases whenever: (1) gross active haematuria was absent; (2) the ureteric orifice had not been resected; or (3) the operating urologist did not have a well-founded suspicion of bladder perforation. In short, intermediate-risk patients, with highly recurrent disease, were offered a 6-week course of MMC and high-risk patients were offered BCG induction plus maintenance if a response was obtained. Follow-up was carried out every 3 months for the first year with cystoscopy and cytology. Cytology plus cystoscopy or ultrasonography were used every 4 months during the second year and every 6 months thereafter.

The TUR specimen was placed in formaldehyde for its fixation before being sent to the pathology laboratory. The laboratory technicians measured, weighed and processed the specimens following the same protocol and using the same precision scale (GF-200, R A&D Co Ltd, Tokyo, Japan), with a lower detection value of 0.001 g. All the TUR specimens obtained at the time of TURBT were included in the analysis. Tumour weight was included in the pathology report along with the standard evaluation.

Statistical analysis

Measurable variables are expressed as mean (SD) if normally distributed or median (interquartile range[IQR]) if not. Quantitative variables were compared using Student's t-test after an evaluation of normal distribution (Kolmogorov-Smirnov) test and equality of variance. Categorical variables are expressed as proportions and were compared using Pearson's chi-squared test with continuity correction or Fisher's exact test, as appropriate. Correlation between the weight and tumour size was performed using Spearman's correlation coefficient.

Recurrence- and progression-free survival curves were estimated by the Kaplan-Meier method, and differences between curves were evaluated with the long-rank test. Patients known to have died from causes unrelated to bladder cancer comprised <5% of the study population and they were censored in the recurrence and progression analysis.

The following methods were used to estimate the weight thresholds:

1. Percentiles: the sample was divided into deciles and the weight threshold was taken as the decile in which a change in risk was detected.
2. Receiver-operating characteristics (ROC) curves: the optimum weight threshold was estimated by the point that maximizes the sum of specificity and sensitivity as expressed by the area under the ROC curve.

We used multivariate Cox proportional hazard regression to assess the association of weight as an independent variable with recurrence. All variables significantly associated with the outcome in the univariate analyses were considered in the maximum

multivariate model as well as corresponding interaction terms. A manual backward modelling strategy was used to eliminate variables from the maximum model to obtain the most parsimonious model to assess the effect of the independent variables on outcome. We tested the proportional hazard assumption by examining log survival plots for different categories against time.

All tests were two-tailed and a P value <0.05 was considered to indicate statistical significance. Statistical analyses were performed using the SPSS 15.0 statistical package for Windows (SPSS Inc, Chicago, IL,USA).

RESULTS

Table 1 lists the clinical and pathological characteristics of the series. The median (IQR) follow-up time was 58 (61.3) months. Seven patients (4.8%) died from causes unrelated to bladder cancer and eight patients (5.5%) were lost to follow-up. The 3-month recurrence-free survival was 97.9%

	Patients with weighed tumours, n=144
Mean (SD) age	68.08 (12.9)
Male gender, n(%)	125 (86.8)
Single tumour, n(%)	109 (75.7)
Grade, n(%)	
G1	74 (51.4)
G2	49 (34)
G3	18 (12.5)
CIS, n(%)	4 (2.8)
Stage, n(%)	
Tx	9 (6.3)
Ta	74 (51.4)
T1	61 (42.3)
Size < 3cm, n(%)	85 (59)
Postoperative single dose MMC, n(%)	86 (59.7)
MMC induction, n(%)	23 (16)
BCG induction, n(%)	25 (17.4)
BCG maintenance, n(%)	15 (10.4)

Table 1. *Patient's clinical and pathological characteristics*

Median (IQR) resected weight was 6 (16) g, with a minimum and maximum weight of 0.03 and 115g respectively. The weight in grams showed a distribution skewed to lower values. Correlation between weight and size of the tumour specimen was notably low (r = 0.32), with a great variability in size for each weight percentile range (Fig 1).

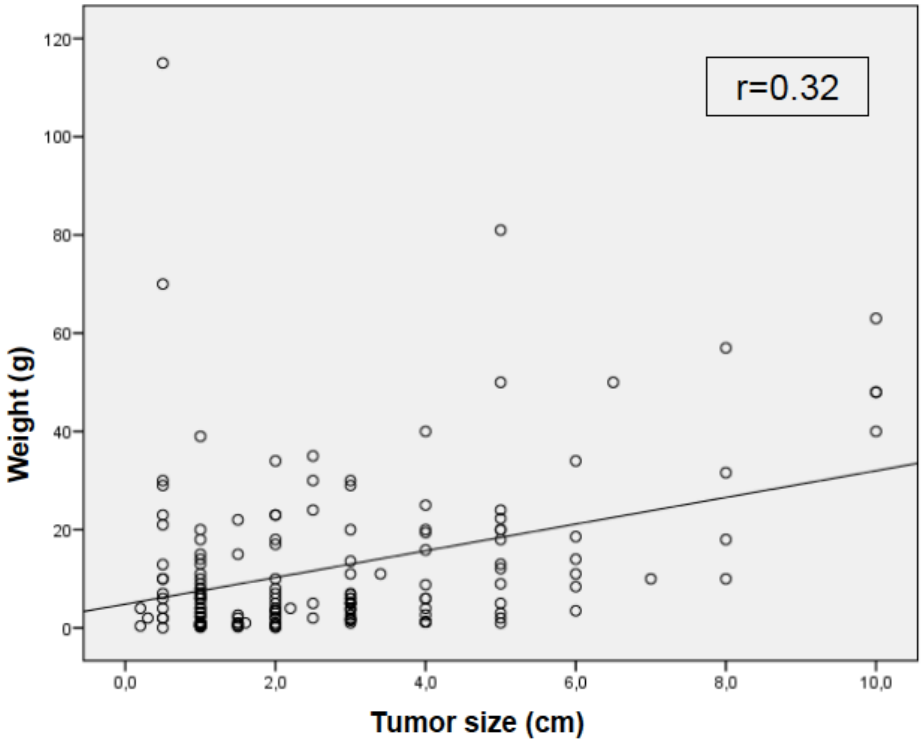

Figure 1. *Correlation between weight and size of the tumour specimen*

Recurrence

The recurrence-free survival rates at 1, 3 and 5 years were 66.7, 49.5, 43.2% respectively. Table 2 shows the association of tumour weight and recurrence.

Weight, g (percentiles)	HR	CI (95%)	p
1.2	2.04	0.39-2.04	0.39
2	2.63	0.51-13.60	0.24
2.4	3.33	0.73-15.08	0.11
5	4.25	0.88-20.48	0.07
6	4.76	1.01-22.44	0.04
8.98	5.78	1.26-26.52	0.02
13.3	5.01	1.09-22.89	0.03
18	5.33	1.14-24.75	0.03
20	2.97	0.59-14.78	0.18

Table 2. *Analysis of the weight thresholds by percentiles*

We found that for a threshold value of 6g the risk of recurrence greatly increased. After controlling for the remaining variables, a weight >6g entailed an increased risk of recurrence estimated at a hazard ratio (HR) of 2.47 (95% CI: 1.19-5.1, P = 0.01 [Fig 2]). Above this weight there was no linear increase in the recurrence risk, which reached a HR of 2.64 (95% CI: 1.048-2.761, P = 0.009) for tumours weighing >18g. The ROC curve for this threshold of 6g showed an area under the curve (AUC) of 0.65 (95% CI: 0.57-0.73), with a sensitivity of 60% (CI 95%: 46.8-70.3) and a specificity of 62% (CI 95%: 49.7-73.2). In the present study, the ROC curve for a tumour size of 3 cm, which is an accepted threshold in the literature, showed an AUC of 0.57 (95% CI: 0.47-0.66) with a sensitivity of 32.9% and a specificity of 78.9% (Fig 3).

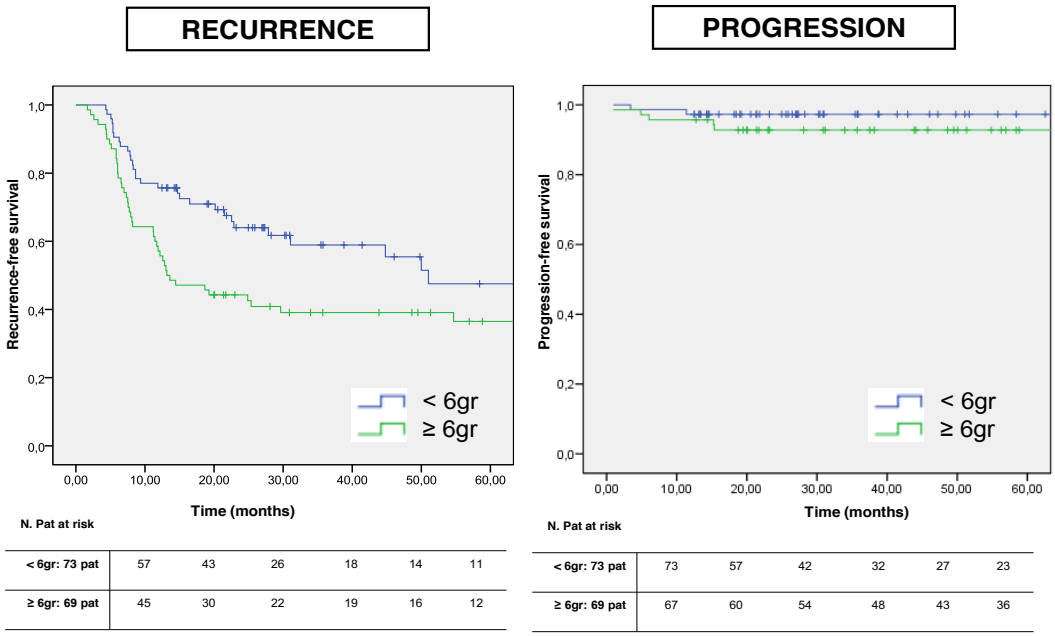

Figure 2. *Recurrence-free and Progression-free survival stratified according to tumour weight*

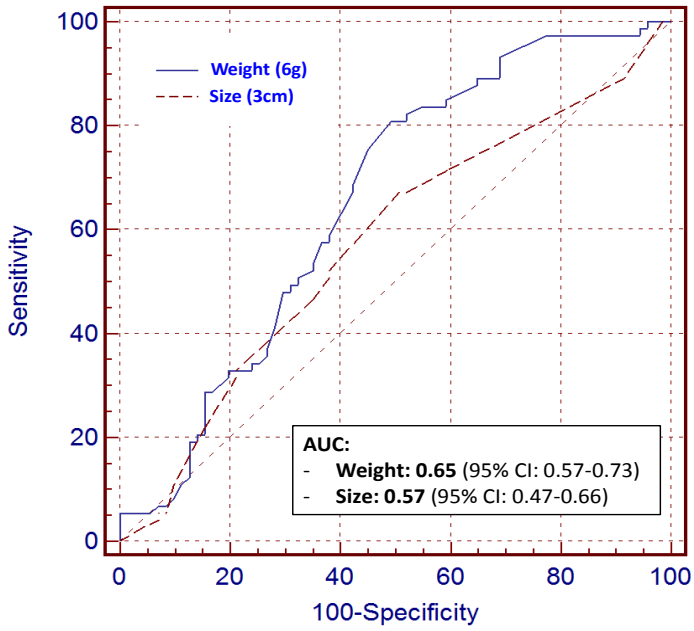

Figure 3*. ROC curve for tumour weight and tumour size*

In the univariate analysis, multiplicity, stage, grade and weight (≥6g) were associated with recurrence (Table 3). Those variables that showed significance in univariate analysis and those that could be clinically relevant were included in the maximum multivariate regression model. After adjusting for size, grade, multiplicity and postoperative single-dose MMC, weight >6g was a predictor of the risk of recurrence with a HR 1.7 (CI 95%: 1.048-2.761), P = 0.03.

Variables	HR	CI (95%)	p
Gender	1.001	0.513-1.951	0.998
Multiplicity	2.833	1.750-4.584	<0.0001
Size <3cm	1.437	0.907-2.277	0.123
Stage	1.891	1.192-3.000	0.007
G3	2.330	1.152-4.713	0.019
CIS	0.714	0.225-2.270	0.568
Postop MMC	0.713	0.438-1.162	0.175
Weight ≥6g	1.775	1.112-2.832	0.016

Table 3. *Univariate analysis*

Progression

Progression-free survival rates at 1, 3 and 5 years were 96.5, 95 and 95%, respectively. Weight was not as an independent predictor of progression in multivariate analysis, nor was it associated with a higher risk of progression (Figure 2). Owing to the limited number of the sample, strong conclusions cannot be drawn at this point.

DISCUSSION

The assessment of the prognostic factors recurrence and progression of NMIBC is of great help in selecting the type of adjuvant treatment after TURBT and in categorizing patients into risk groups that enable us to compare different treatment regimens[10]. This categorization should eventually provide clinically relevant information about the length of adjuvant treatment[11] or for the change in the therapeutic strategy towards radical surgery for those patients harbouring non-responding high-risk tumours [12].

In addition to the EORTC risk calculator [2] and the CUETO tables [6], a nomogram has been proposed to predict the recurrence risk based on age, gender, cytology and urinary nuclear matrix protein 22 in patients with NMIBC [13].

In the landmark reports by Millan et al [1,7] and the later meta-analysis by Sylvester et al.[2], the tumour burden, expressed either by the size of the tumour or by the number of tumours, was the most important prognostic factor.

In the report by Sylvester et al.[2], size provides a 17% (3/17) relative value of the total score. As an example of the importance of size in the risk assessment, a single primary pT1G2 without CIS of 2.5cm would have a 1- and 5-year recurrence risk of 24% and 46%, respectively. If this same tumour were 5mm larger, i.e. 3cm, the 1- and 5-year recurrence risk would be 38% and 63%, respectively. This means that a 58% and 36% risk increase at 1- and 5-years is calculated by only a 5mm increase in size which is measured by a non-objective way and subject to significant interobserver variability.

This observer-dependent measurement could be excluded by using an objective, measurable and reproducible variable such as the weight of the complete TUR specimen [14] following strict quality control criteria[15].

No information is available on how size was measured in any of the trials included in the meta-analysis by Sylvester et al. [16–21]. In the study by Millan et al. [1], size was categorized into three groups; however, significance of the recurrence risk (HR 1.6) was only reached for a size threshold of 3cm. In the present study, we noted a relationship between weight and the risk of recurrence; tumours weighing >6g had a higher risk of recurrence with a HR of 1.7.

Tumour volume and the pattern of growth are critical issues in the biology of the tumour. This growth rate has also been correlated with the potential for recurrence and the development of metastasis [22].

The weight of the resected specimen more accurately represents the real tumour volume than does tumour size. By adding the weight of multiple resected tumours, it is possible to obtain the total tumour volume of a commonly multifocal disease, as is the case of NMIBC. In addition, as opposed to visual observation, weight of the specimen informs us of the total tumour volume and not only of the exofitic part of the neoplasm. In the present study, a tumour with the same size had significant differences in weight owing to the configuration of the lesion. Solid tumours were denser and weighed more (median 16.5g) than papillary lesions (median 6g), p 0.002.

Progression of NMIBC is also influenced by other factors: accuracy of the staging by the pathologist, use of random biopsies, definition of progression, quality of the TUR, use of adjuvant therapy and duration of follow-up as well as some molecular expression of the tumour [23]. These factors may have influenced the lack of significance of weight in predicting progression.

External validity assessment was done by testing the homogeneity of the study group with the overall series of patients operated on in our hospital with NMIBC. This group showed no significant difference from the global population in any of the variables, which makes both groups clinically similar. No significant differences were found either between the recurrence-free survival of the overall series and the study group at 1, 3 and 5 years with a HR of 1.20 (95% CI: 0.93-1.57) P = 0.15, or progression-free survival at 1, 3 and 5 years with a HR of 1.13 (95% CI: 0.48-2.63) P = 0.70.

One limitation of this study is related to sample size and therefore to the accuracy of our data. The power of our study for this sample size was estimated at 95%. Moreover, the number of relapsed patients in the series (73 patients) did not represent a limitation for inclusion of variables in the logistic regression model. There are other limitations to the present study that should be acknowledged, including the matter of resection completeness. All procedures were performed by eight experienced urologist or supervised residents with the goal of achieving a complete TUR of all visible tumour in all cases. The resection of some healthy tissue is performed in all resections so we must concede that the weight values were overestimates; however, this applies to all cases and should not have led to bias. Nevertheless, the lack of randomization makes it necessary to confirm these results in future prospective studies.

CONCLUSIONS

In conclusion, the weight of the resected specimen after TUR of NMIBC is a prognostic variable of recurrence that has not previously been described. Standardized complete TUR allows us to obtain a measurable predictor unrelated to observer subjectivity that can eventually be used in the current risk calculator should our findings be confirmed. In the present series, those tumours that weigh > 6g had a 1.7-fold risk of recurrence

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SAFETY OF AN ACTIVE SURVEILLANCE PROGRAM FOR RECURRENT NON-MUSCLE-INVASIVE BLADDER CARCINOMA.

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ABSTRACT

Objectives: To report our experience with a select group of patients with low-risk tumours included in an observation and monitoring program after the diagnosis of a recurrence.

Materials and Methods: We performed a prospective cohort study in patients diagnosed with recurrent, nonmuscle-invasive bladder cancer maintained under an active surveillance protocol. The inclusion criteria were papillary tumours with negative cytology findings, previous nonmuscle-invasive tumour (Stage pTa, pT1a), grade 1-2, size <1 cm, and number of tumours <5. No symptomatic patients or those with carcinoma in situ or grade 3 tumours were included. A retrospective analysis of a control group of patients with clinical characteristics similar to patients on active surveillance, but who underwent transurethral resection immediately after the recurrence was diagnosed was also performed.

Results: The data from 64 patients (70 observation events) were analyzed. The mean patient age was 66.7 years. The median follow-up was 38.6 months. The median time patients remained in observation was 10.3 months. The tumour histologic features before observation were Stage pTa in 77.1%, Stage pT1a in 22.9%, grade 1 in 67.1% and grade 2 in 23%. After 10.3 months, 93.5% of the patients had not progressed in stage and 83.8% had not progressed in grade. None of the patients experienced progression to muscle-invasive stage. A comparison between the rates of progression in the study and control groups showed no statistically significant difference.

Conclusions: Patients with recurrent, small (<1 cm), nonmuscle-invasive bladder tumours can be safely offered monitoring under an active surveillance protocol with minimal risk of progression in either grade or stage, thus reducing the amount of surgical intervention they might undergo throughout their life.

INTRODUCTION

Nonmuscle-invasive bladder tumours are a very heterogeneous group, ranging from papillary tumours only affecting the mucosa and presenting as low grade (Stage Ta, G1) to high-grade tumours (Stage T1, G3) with associated carcinoma in situ (CIS). These tumours are associated with a high degree of recurrence throughout their follow-up[1], and they are usually treated by resection or fulguration of the lesions[2], in addition to some form of chemotherapy or inmunoprophylaxis.

Software tools are available that can help to predict the behaviour of these tumours in terms of their risk of progression and recurrence[3]. However, very little scientific evidence is available regarding the actual progression rates if surgical treatment is delayed in select patients with tumours considered low risk owing to their clinical characteristics[4,5].

An active surveillance program has been available for several years at our institution for patients with low-risk bladder cancer. This surveillance option was specifically intended for patients with recurrent nonmuscle-invasive bladder tumours, for whom, because of the clinical history or tumour characteristics, we did not believe that immediate resection was necessary after diagnosis. This protocol was also designed to reduce the number of surgeries throughout the patients' lifetime. This approach has been previously described by Soloway et al.[4] in 2003 who concluded that, in selected cases, active surveillance is a safe and valid therapeutic alternative. The goal of the present study was to evaluate the long-term oncologic safety and to determine the risk of tumour progression among patients enrolled in an active surveillance program for low-risk bladder cancer.

MATERIALS AND METHODS

A prospective cohort study of patients who had undergone surgery at our hospital from 1999 and 2006 was initiated. Patients deemed to be candidates were offered entry into the study after the pathologic report showed nonmuscle-invasive tumour and if they presented with tumour recurrence during the follow-up period. We included these patients in an active surveillance program after the patients provided fully informed consent. They were allowed to undergo surgery if they chose at any point during the observation period.

The inclusion criteria for the observation program were recurrent papillary tumours with a previous finding of nonmuscle-invasive urothelial carcinoma, Stage pTa and pT1a (extending into the lamina propria but above the level of the muscularis mucosa), low or intermediate grade (G1-G2), <1 cm in size, and with <5 tumour sites. No patients with a history of a high-grade tumour (G3), CIS, or positive cytology findings were included in the observation and monitoring program.

All patients included in the observation group underwent close monitoring with cytology and flexible cystoscopy every 3-4 months. All pathologic studies were performed by a single experienced uropathologist and fully dedicated cytologists.

The patients discontinued the observation period and underwent transurethral resection when they presented with an increase in the number and/or size of the lesions, symptoms (mainly hematuria), or if the surveillance urine cytology findings were positive for malignancy.

During the study period, active surveillance was not used for all the patients diagnosed with tumours of these characteristics. Therefore, we decided to retrospectively review the data from patients in whom immediate transurethral resection was performed after the diagnosis of tumour with clinical characteristics identical to those of our observation group.

The variables included in our statistical analyses were the interval from the initial diagnosis to entry into the observation period, tumour size, number of tumours, interval that the patient remained in observation, reason for discontinuing observation, progression stage and/or grade of the tumour. The qualitative variables are presented by frequency distribution and the quantitative variables by the mean ± SD and median with the interquartile range. The comparison of qualitative variables was done using the Chi squared test. The probability of recurrence was studied using a survival analysis by the Kaplan-Meier method. The significance level in all the hypothesis tests was P = .05. The software used for the analysis was Statistical Package for Social Sciences, version 12 (SPSS, Chicago, IL).

RESULTS

A total of 273 patients with nonmuscle-invasive tumours had undergone surgery at our hospital from 1999 to 2006. A series of 64 patients with a total of 70 observation events (some patients entered the observation program several times throughout their follow-up period) was studied. The mean age was 66.7 ± 13.1 years, and 82.9% of the patients were male. The median interval from the initial diagnosis to entering the observation period was 17.3 months (interquartile range 3.16). The median follow-up for all patients in the study was 38.6 months (interquartile range 36.7). The median interval during which the patients remained in observation was 10.3 months (range 1.13 – 47.5). The histologic features before observation were: Stage Ta in 77.1% of the patients, Stage T1a in 22.9%, G1 in 67.1% and G2 in 23%.

The most common reason for discontinuing the observation period (58.6%) was an increase in the number and/or size of the tumours. The other reasons were symptoms (4.3%), positive cytology onset (2.9%), increase in the size of the lesion and positive cytology (4.3%), non-cancer-related death (4.3%) and patient request (1.4%). The rest of the patients (24.2%) were still under observation at the data analysis. No patient left the observation program because of poor compliance with the established follow-up protocol.

The pathologic findings at entry to the observation period and after completing this period are shown in Table 1. After remaining in observation for a median time of 10.3 months, 93.5% of the patients had not progressed in stage and 83.8% had not progressed in grade (Fig. 1). None of the patients experienced progression to muscle-invasive tumour. Only 3 patients in the whole series presented with progression to a high-grade

tumour (G3) or presented with associated CIS. No adjustment for gender was made because the low number of women in the study (n = 5) did not allow us to draw any conclusions.

	After Observation						
Before Observation	**Ta G1-2**	**T1 G1-2**	**G3/CIS**	**T0**	**Tx**	**NA**	**Total**
Ta G1-2	24	3	1	3	6	18	54
T1 G1-2	6	1	2	0	0	7	16

CIS = carcinoma in situ; NA = pathologic data not available because patient was in observation period or because of noncancer-related death)

Table 1: *Histologic findings before and after observation period*

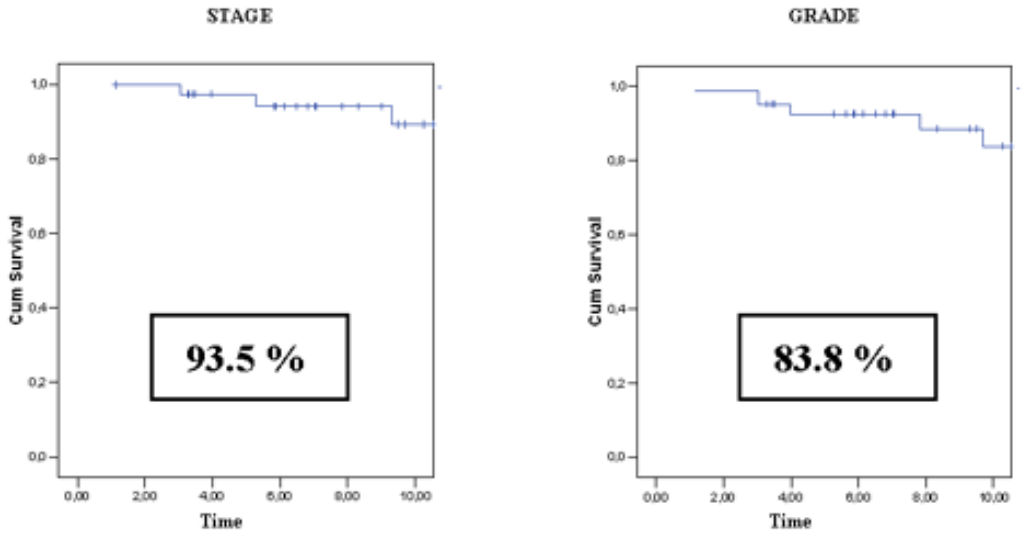

Figure 1*: Probability of progression in stage and grade analyzed by Kaplan-Meier method*

Table 2 lists the data from the group control of patients in whom immediate transurethral resection was performed after the diagnosis of tumours with clinical characteristics identical to those of our observation group. In the control group, 11.2 % of the patients presented with progression in stage (compared with 6.5% of the observation group), and 7.82% presented with progression in grade (compared with 16.2% in the observation group). Only 4 patients (4.40% vs 4.28% in the observation group) developed progression to G3 or presented with associated CIS. No significant differences were found when we compared the progression rates in grade and stage in the 2 groups. In the control group, progression to infiltrating tumour was found in 2 patients.

	At Recurrence						
Initial Tumour Stage and Grade	**Ta G1-2**	**T1 G1-2**	**G3/CIS**	**T0**	**Tx**	**T2**	**Total**
Ta G1-2	47	6	2	6	7	1	67
T1 G1-2	6	9	2	3	3	1	23

CIS = carcinoma in situ.

Table 2: *Group of patients with similar characteristics who were operated on immediately after diagnosis of a recurrent tumour*

DISCUSION

Nonmuscle-invasive bladder tumours are associated with a high degree of recurrence throughout the follow-up period[1,6]. Transurethral resection is the therapeutic option of choice, not only because it eradicates existing visible bladder lesions, but also because it provides sufficient material for a correct diagnosis and tumour graded determination. The method of surgical resection also provides histologic information that makes it possible to establish prognostic information. Some form of chemoprophylaxis (immediate single-dose mytomicin C) for low- to intermediate-risk patients or immunoprophylaxis with bacile Calmette-Guerin for intermediate- to high-risk patients is commonly used. Repeat transurethral resection is only performed in our practice for patients with an initial pT1G3 or whenever muscularis propria is absent in the surgical specimen.

Patients with bladder cancer will often undergo several transurethral resections to treat recurrent lesions, which can be associated with complications and side effects. The low likelihood of progression and the indolent nature of certain types of bladder tumours will have a negligible effect on survival in select patients[7].

It has been shown that in patients with negative cytologic findings, there is a high correlation between the cystoscopic findings and the histologic features of the tumour is high, with an accuracy of ≤98%[8]. The cystoscopic findings of bladder cancer can also predict for muscle invasion[9]. It has been described as accepted practice to perform office fulguration of small recurrent papillary tumours. Fulguration achieves sufficient control in this type of tumour[10]. At our centre, fulguration of these recurrent tumours is not the regular practice, because we believe that no sort of active

treatment is needed for this tumour type according to its biologic behaviour. In addition, we believe that active surveillance can be conducted in selected patients with recurrent tumours that we consider to be low risk to avoid repeated surgery.

The observation of these tumours, without active treatment, is a common clinical practice; however, although routinely performed by some urologists, it has not been included in any clinical guidelines. Therefore, to begin an active surveillance program, no inclusion or exclusion criteria have been determined beyond those reasonably assumed by the urologist who evaluates the specific comorbidity of each patient and the risk of progression and/or recurrence of each tumour.

The decision to include patients in this program was not determined by patient age or associated comorbidities, but rather by the clinical characteristics of the tumour (cystoscopic appearance of a low-grade tumour) and the absence of symptoms, mainly hematuria, and negative cytology findings. In all cases, the individual clinical features were taken into account, and they were considered a very important criterion to reach an agreement with the patients about the course of action, after explaining the risks and benefits and ensuring that they understood that an observation program was not included in the recommendations of the clinical guidelines approved by the different urologic associations.

The tumour grade was the most important of the inclusion criteria. It is well established that the risk of progression of low-grade, Stage Ta lesions to muscle-invasive cancer is small, generally around 5-10%. These tumours do not share the biologic potential of tumours that invade the lamina propria (Stage T1), because the latter have a greater

probability of muscular invasion and they tend to be of a higher cytologic grade. Including patients with tumours that invade the lamina propria in this observation program would be questionable. Nevertheless, a different prognosis can be made according to the depth of lamina propria invasion, beyond the muscularis mucosa (T1b), with a probability of progression of ≤53% compared with those with more superficial invasion of the lamina propria (T1a), whose probability of progression is similar to that of those with Stage Ta, about 5%[11]. We therefore decided to include these selected patients with Stage T1a in our group because they were not at a greater risk than other patients with Stage Ta tumours.

Our group of patients remained in observation for a median of 10.3 months. The most common cause to proceed to surgery was an increase in the tumour number or size. The chronology of the tumour occurrence is an aspect that must be taken into account when deciding on the therapeutic options. Disease recurrence is closely linked to the duration of the period free of disease after the first transurethral resection; however, almost 50% of the patients will undergo another transurethral resection during their lifetime and almost three quarters will undergo ≥3 additional operations. It is therefore a sensible approach to regard stability in the size and number of tumours at cystoscopy during the follow-up period as a follow-up criterion.

To our knowledge, this is the largest series published on patients with nonmuscle-invasive tumours under observation[4,5,12–14]. The results in the series by Soloway et al.[4] (which included Stage T1 and high-grade tumours) were similar to ours (6.7% with progression to high grade vs 4.28% in our series). In another study by Gofrit et al.[5], no progression in any of the high-grade tumours was detected; however, we must

consider that this was a more homogeneous series, because all initial tumours were Stage TaG1-2 (Table 3).

Investigator	n	Median Time in Observation (mo)	Pathologic Findings Before Observation	Progression to High Grade (%)
Soloway et al.[4], 2003	44	10.09	Ta-T1 / G1-3	6.7
Martínez Caceres et al. [12], 2005	15	5.76	Ta-T1 / G1-3	6.67
Gofrit et al. [5], 2006	38	13.5	Ta / G1-2	0
Pruthi et al. [13], 2008	22	NA	Ta-T1/ G1-3	9
Present Study	70	10.3	Ta-T1a / G1-2	4.28

NA = not available.

Table 3*: Comparison between progression rates in grade and stage for each group*

The choice of 5 papillary tumours as a maximal inclusion criterion was arbitrary. Low-grade bladder tumours are normally multifocal, and they can appear throughout the urothelium, simultaneously or over time, with the rest of the mucosa endoscopically and histologically normal. This fact speaks in favour of the biological indolence of the disease and must be differentiated from the concept of diffuse lesion in the urothelium with adjacent involvement of premalignant (dysplasia) or malignant (CIS) lesions. The progression rate in these low-grade multiple tumours was comparable to that described in other series in which resection was performed immediately after the diagnosis.

The follow-up of the patients in the present series consisted of cystoscopy and cytology every 3-4 months for the first year. We consider that flexible cystoscopy is a well-tolerated examination with a much lower rate of complications than surgery and with a

high acceptance of ≤99.5[15]. Once the treatment alternatives were explained, a high percentage of patients preferred to undergo close monitoring by cystoscopy and to delay the surgery for as long as possible. At the end of the recruitment period for the present study, we modified the schedule of endoscopic examinations. In patients who had completed their first year follow-up, the studies were done on an alternating basis between ultrasonography and cystoscopy plus cytology, and in these cases, the follow-up intervals were increased to every 6 months. Bladder ultrasonography is an accepted diagnostic modality as recognized in current clinical guidelines[16] and allows for the detection of growth or permanence as low-burden disease while remaining undetectable on ultrasound.

We consider urinary cytology a pivotal examination for patients participating in an observation and monitoring program. The cytologic identification of high-grade lesions is diagnostically important and offers great value as a prognostic risk factor. Its performance is excellent, with a sensitivity of 90% in these high-grade cases and a specificity of 98% to 100%. In our program, it was therefore a critical point to discontinue the observation, regardless of the number and/or size of the lesions being controlled. Our experiences with other markers such as BTA TRAK (bladder tumor antigen) or NMP22 assays have not changed our attitude, given their high rate of false-positive results in the context of infection, lithiasis, or instrumentation. In the end, we have always resorted to selective urine cytology to support our approach to a given case[17].

Finally, the criteria for discontinuing the observation included the symptoms caused by the tumour. In the case of hematuria, even if it was self-limited, our approach was to remove the patient from active surveillance and propose surgery.

This active surveillance program was not used on all patients diagnosed with a recurrence during follow-up at our centre. The patients were included in this study on the basis of the attending urologist's preference. This has enabled us to retrospectively review and select patients with identical clinical characteristics who had undergone immediate resection after diagnosis, with the finding that the incidence of progression in grade and stage in these patients was no different from that of the patients in our observation group.

A limitation of this study was the lack of randomization between groups, which would have allowed for more robust conclusions to be drawn. To minimize the selection bias due to nonrandomization, the histopathologic characteristics of both groups, as listed in Table 2, were equivalent in terms of grade and stage.

The benefits achieved with this practice were mainly a reduction in the number of resections that patients would undergo in their lifetime, with the attendant potential complications. Postoperative bleeding and bladder perforation are the most common immediate complications and vesicoureteral reflux, bladder retraction, and urethral stenosis the most common later complications [6]. This potential benefit was difficult to quantify with the current study design, and only a randomized study would be able to answer that point. The goal was to avoid excessive treatments as much as possible without putting patients into danger of an adverse clinical course. Although it was not

an objective of our study, this practice also involves an added economic benefit by sparing the patients the expense of a surgical intervention.

CONCLUSIONS

Patients with small recurrent nonmuscle-invasive bladder tumours of a low-grade cystoscopic appearance can be placed into an observation protocol without an increased risk of progression either in grade or stage, thus reducing the amount of surgery that patients undergo throughout their lifetime, as well as reducing potential complications associated with such procedures.

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LONG-TERM ONCOLOGICAL OUTCOMES OF AN ACTIVE SURVEILLANCE PROGRAM IN RECURRENT LOW GRADE Ta BLADDER CANCER

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ABSTRACT

Objectives: Over the last 2 decades, there has been a major increase in active surveillance (AS) as a therapeutic alternative in urological tumours regarded to be of low risk. Owing to the findings of significant clinical outcomes in our series, this report presents an update of our AS program in patients with recurrent non-muscle invasive bladder tumour. The objective was to confirm the oncological long-term safety of this protocol and to determine possible variables associated with progression.

Materials and Methods: Cohort of patients included in AS between 1999 and 2014. Inclusion criteria: recurrent papillary tumours, previous pTa-pT1, G1-G2, shorter than 1cm, and fewer than 5 tumour sites. Exclusion criteria: prior G3, CIS (carcinoma in situ), or positive-result cytology.

All patients underwent close monitoring with flexible cystoscopy every 3 to 4 months for the first 2 years. After this time, follow-ups were conducted every 6 months, alternating between cystoscopy and ultrasound. Urinary cytology was performed at all visits.

Results: In all, 252 AS periods in 186 patients were studied, with a median follow-up of 6 years. Out of all periods, 203 (80.6%) underwent active treatment.

After remaining under observation, 86.4% had not progressed in stage, and 79.3% in grade. Of these patients, 4 experienced progression to T2: all of them were previously T1G2.

Conclusions: AS in a high-selectivity group of patients with recurrent non-muscle-invasive bladder tumour is feasible and oncologically safe in the long term. Patients with previous history of T1 should not be included in AS protocols even when very small recurrences are diagnosed.

INTRODUCTION

The natural history of non-muscle invasive bladder cancer (NMIBC) is characterized by the high relapse rate presented by these neoplasms during follow-up, along with a smaller likelihood of stage progression [1]. Depending on the clinical features of the tumour, a 5-year recurrence rate of 30 to 78% has been estimated by the risk calculator of European Organization for Research and Treatment of Cancer [2]. This means that patients with this condition undergo multiple resections throughout the follow-up of their disease. Although transurethral resection of bladder tumour (TURBT) is the most common surgical procedure in urological clinical practice [3], it is not free from morbidity, and these patients are at risk of both perioperative and long-term complications, with a significant effect on the patient´s quality of life [4].

Our institution has performed an ongoing protocol since 1999 for active surveillance (AS) in small, recurrent NMIBCs. In 2009, we published the results of our initial experience with 64 patients and a median follow-up of 38.6 months [5]. Our experience and that reported by other authors [6–8] allowed us to continue our study by recruiting more patients into this mode of management.

Owing to the findings of significant clinical outcomes, this article presents an update of our series, which to date has the largest number of patients and longest follow-up of any series published in the literature. The objective was to confirm the oncological long-term safety of this protocol and to determine possible variables associated with grade or stage progression.

MATERIALS AND METHODS

This is a prospective cohort of patients included in our institutional bladder cancer AS database between 1999 and 2014, after a fully informed verbal consent had been obtained and filed in the electronic medical record. This protocol was approved by our Hospital's Institutional Review Board.

All patients included in this protocol had an initial urothelial bladder cancer pTa-T1 G1-2 diagnosed by a first TURBT, and during their follow-up developed a recurrence considered to be of low risk by its cystoscopic appearance. At the time when the recurrence was detected, patients were offered to be included in a surveillance protocol to delay the surgery until a progression of the lesion was noted according to the criteria described later. In patients with multiple recurrences, surveillance was proposed whenever the cystoscopic appearance of the lesion fulfilled the inclusion criteria describe earlier. For this reason, a patient could be included under surveillance more than once during follow-up and as a result, the number of events of surveillance in the results section is higher than the number of patients included in the study.

The following inclusion criteria were required to enter the study: recurrent papillary tumours with previous histologically proven non-muscle invasive urothelial carcinoma, pTa or pT1 stage, low or intermediate grade (G1-G2, WHO 1973), less than 1 cm in main size of any lesion, and fewer than 5 tumour sites. Comorbidities were not taken into account when patient selection was performed.

Patients with a pT1 tumour were included only when muscle was present in the first specimen or in the Re-TUR specimen if needed. A second resection in T1 tumours was considered when the initial resection was incomplete, the tumour was larger than 3 cm, or there were multiple tumours, or when the pathologist reported that the specimen contained no muscle tissue. Patients were excluded whenever any of the following criteria was present: prior history of a high-grade tumour (G3), carcinoma in situ (CIS), or positive-result cytology.

All patients included underwent close monitoring with flexible cystoscopy every 3 to 4 months for the first 2 years. After this time, follow-ups were conducted every 6 months, alternating between cystoscopy and ultrasound. Urinary cytology test was performed at all visits. None of the patients was treated with intravesical treatment during the surveillance period, although they could have received chemo/immunotherapy before the inclusion depending on the characteristics of the disease. All pathological studies were performed by 2 experienced uropathologists and cytologists.

Patients discontinued the observation period and underwent transurethral resection (TUR) when they presented an increase in the number or size of the lesions, symptoms (mainly hematuria), a positive urine cytology test result during surveillance, or if the patient so elected at any time during the observation period.

As a response variable we assessed grade or pathological stage progression at the beginning and at the end of the observation time. Grade progression was defined as

conversion from G1 to G2 or any new-appearance G3. Stage progression was defined as growth from Ta to T1 or any T2 or higher stage.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 and STATA 12.0. Time under surveillance was studied considering competing risk. In these cases, the appropriate estimate of the event probabilities is the cumulative incidence. Cumulative incidence function (CIF) for undergoing active treatment estimates was obtained using competing-risks regression based on the proportional subhazards model of Fine and Gray. The standard error of hazard ratios was estimated considering intrasubject variability, in case of multiple periods on the same patient. Death and tumours no longer evident during follow-up were treated as competing events. Censored cases were regarded as those remaining under surveillance at the end of the study, as well as patients who were lost to follow-up during the surveillance period. Patients lost to follow-up were censored at the time of their last visit with the status at the last observation carried forward. The assumption of proportional hazards in the Cox regression model was tested with Schoenfeld residuals and was found to be valid. No evidence for interactions between the study variables was observed. Univariate and multivariate Mixed Models Generalized were used to analyse risk factors associated with stage progression or grade progression, with a subject random effect. Odds Ratios (OR) were estimated with generalized estimated equations [9]. In multivariate models, the variables nonstatistically significant were eliminated in a backward-step method. All tests were considered bilateral and the level of statistical significance was set at 0.05.

RESULTS

In all, 252 AS periods in 186 patients were studied, with a median follow-up of 6 years (interquartile range: 4-9.1). The number of periods was higher than the number of patients because each patient could undergo AS more than once during follow up. The series included 161 men and 25 women, with a mean age of 66.6 years (SD = 11.8).

Pathological characteristics before entry into observation were TaG1 131 (51.9%), TaG2 54 (21.4%), T1G1 25 (9.9%) and T1G2 42 (16.7)%. The mean time from the last TURBT until entry into the surveillance program once a recurrence was detected was 11.8 months (SD = 13.4), whereas the mean time from each patient's first TUR was 24.3 months (SD = 27.1). The characteristics of these patients in the diagnostic TURBT are presented in Table 1.

Out of all periods, in 203 (80.6%), active treatment was performed, with a median treatment-free survival after diagnosis of recurrence and entry into AS of 13.4 months. Of these, 17.1% (43 patients) remained under surveillance for more than 24 months and 8.7% (22 patients) remained under AS for more than 3 years.

According to previous stage and grade, median CIF time was 12.6 months in T1 and 12.9 months in Ta, P = 0.375. Median CIF time was 11.4 months in G1 and 13.8 months in G2, P = 0.899.

Variables	N (=186)
Age, y	66.6 (11.8) *
Sex (male)	161 (86.6%)
No. of tumours (single)	118 (63.4%)
Size (< 3cm)	132 (71.0%)
Stage	
Ta	124 (66.7%)
T1	62 (33.3%)
Grade	
G1	109 (58.6%)
G2	77 (41.4%)
Postoperative single-dose MMC (yes)	129 (69.4%)
Previous adjuvant treatment (MMC/BCG)	
MMC	54 (29%)
BCG	26 (14%)

BCG = Bacillus Calmette-Guérin; MMC = mitomycin C.

*Data presented in mean (SD)

Table 1. *Characteristics of the series at initial TURBT*

During the follow-up period, there were 11 non-cancer-related deaths (4.4%) and 13 (5.2%) losses of follow-up. The reasons for dropping out of the program are presented in Table 2.

Reason for dropping out of active surveillance	Time under surveillance					Total N, %
	<6 mo	6-12 mo	12-24 mo	24-36 mo	>36 mo	
Increased lesion number or size	36	47	45	15	13	156 (61.9)
Positive-result cytology	4	7	7			18 (7.1)
Increased number/size and positive-result cytology	5	6	7	3	1	22 (8.7)
Non-cancer-related death during the surveillance period		4	6	1		11 (4.4)
Loss of follow-up during the surveillance period	2	3	6		2	13 (5.2)
No longer evident tumour during follow-up	4	2		2	1	9 (3.6)
Symptoms	1	1	2			4 (1.6)
Patient request	2		1			3 (1.2)

Table 2. *Reasons for dropping out of the active surveillance program. Data are presented according to the time under surveillance*

After remaining under observation, 171 surveillance periods (86.4%) had not progressed in stage, and 157(79.3%) had not progressed in grade. Of these patients, 9 patients (3.6%) progressed to G3, 6 patients (2.4%) progressed to CIS, and 4 patients experienced progression to T2 (Table 3). All of these patients were previously T1G2 less than 3mm in size when they were entered to the program and were submitted to

radical cystectomy when progression was detected after an increase in the number of tumours in 3 of them and a positive cytology in 1 of these. The other patient was temporarily lost to follow-up because of non-compliance with the program. Cystectomy specimen showed a pT2G3 urothelial bladder cancer in all 4 patients with node involvement in 2 of them.

Before active surveillance	**After active surveillance**										
	TaG1	**TaG2**	**T1G1**	**T1G2**	**G3**	**CIS**	**T0**	**Tx**	**T2**	**NA**	**TOTAL**
TaG1	58	20	10	4	2	4	9	7	0	21	131
TaG2	8	13	1	8	1	1	6	8	0	9	54
T1G1	6	2	3	1	0	0	2	3	0	8	25
T1G2	3	4	1	6	6	1	0	2	4	16	42

NA: Pathological data not available because of patient remaining under surveillance period, non-cancer-related death, or loss of follow-up

Table 3. *Histological findings before and after active surveillance period*

Univariate analysis for progression in grade is presented in Table 4. In multivariate analyses, factors related to an increased risk of progression in grade were multiplicity OR = 2.08 (95% CI: 1–4.35; P = 0.5), previous stage OR = 0.25 (95% CI: 0.10-0.62; P = 0.003), previous grade OR = 3.09 (95% CI: 1.38-6.9; P = 0.006), age OR = 1.04 (95% CI: 1-1.07; P = 0.032), and time since initial TURBT OR = 1.02 (95%CI: 1.01-1.04; P

= 0.008). None of the factors studied were associated with the risk of progression in stage (Table 4).

	Progression T					Progression G				
	YES	NO	OR	95% CI	P	YES	NO	OR	95% CI	P
Age, y, X ± SD	68.6 ± 12.1	65.1 ± 12	1.03	0.99 - 1.07	0.182	66.7 ± 11.4	65.3 ± 12.2	1.01	1 - 1.03	0.043
Sex, n (%)			0.89	0.31 - 2.6	0.836			0.71	0.3 - 1.7	0.442
Male	23 (13.5)	148 (86.5)				34 (19.9)	137 (80.1)			
Female	4 (14.8)	23 (85.2)				7 (25.9)	20 (74.1)			
Time since last TURBT, mo, X ± SD	10.2 ± 8.7	10.3 ± 8.3	1	0.95 - 1.05	0.941	12 ± 8.5	9.9 ± 8.3	1.03	0.99 - 1.07	0.156
Time since initial TURBT, mo, X ± SD	30.2 ± 31.1	29.5 ± 27.5	1	0.99 - 1.02	0.907	38.1 ± 31	27.4 ± 26.7	1.01	1 - 1.03	0.043
Multiple/single tumour, n (%)			1.17	0.53 - 2.59	0.701			2.11	1.07 - 4.16	0.031
	13 (12.7)	89 (87.3)				14 (14.6)	82 (85.4)			
Multiple	14 (14.6)	82 (85.4)				27 (26.5)	75 (73.5)			
Single										
Tumour size, cm, X ± SD	0.4 ± 0.2	0.4 ± 0.2	0.63	0.1 - 4.14	0.627	0.4 ± 0.2	0.4 ± 0.2	1.65	0.47 - 5.76	0.432
Previous Stage, n (%)			1.7	0.55 - 5.28	0.36			0.6	0.28 - 1.29	0.186
Ta	23 (14.8)	132 (85.2)				29 (18.7)	126 (81.3)			
T1	4 (9.3)	39 (90.7)				12 (27.9)	31 (72.1)			
Previous Grade, n (%)			0.55	0.25 - 1.25	0.154			1.97	0.89 - 4.35	0.093
G1	15 (11.7)	113 (88.3)				31 (24.4)	96 (75.6)			
G2	12 (17.1)	58 (82.9)				10 (14.1)	61 (85.9)			
Number of previous TUR	2 (1 - 3)	2 (1 - 3)	0.95	0.78 - 1.15	0.576	2 (1 - 4)	2 (1 - 3)	1.15	1.01 - 1.3	0.037

Table 4*. Univariate Analysis*

DISCUSSION

Over the last 2 decades, there has been a major increase in AS as a therapeutic alternative in urological tumours regarded to be of low-risk. The concept of AS as a management strategy in bladder cancer began 10 years ago; although as yet few series have been published, watchful waiting in patients with very small recurrent tumours has been shown to be oncologically safe after short or mid-term follow-up [5, 8].

In 2003, Soloway et al. [6] published the first series of patients with small recurrent tumours under AS. Since then, the few series published have had short follow-ups and heterogeneous inclusion criteria. In 2006, Gofrit et al. [8] published the first homogeneous series of low-risk patients with clearly defined inclusion criteria for low-risk tumours (recurrence of previously Ta G1-2 tumours, size <1cm, negative-result cytology test, and exclusion of previous G3). The results of these series in progression rates of grade or stage are similar to those of the present study. However, none of them had previously reported a case of progression to muscle-invasive disease.

We previously showed that our series of median- or low-risk tumours, with homogeneous and strict inclusion criteria, experienced a very low progression rate in grade and that progression to muscle-invasive stage did not occur. In fact, there were no differences in grade or in stage progression when compared to a control group of patients of similar pathological characteristics treated immediately after diagnosis [5].

The present article provides an update on our series with a mean follow-up time of 6.8 years, which confers a significant robustness to our results. In all, 4 patients experienced progression to T2 stage. All of those cases were previously T1G2. We would like to emphasize that patients harboring a pT1 lesion were included in our study only when very restrictive conditions were present: no G3, no concomitant CIS, healthy muscle present at initial or Re-TUR specimen, and small recurrences during follow-up (all cases of progression in our series were <3mm). Despite these restrictions, and in light of the results, our protocol has been changed, and patients with previous T1 are no longer included in this program. An early recurrence may result in worse prognosis of the disease, so this should also be considered as an exclusion criterion for these programs.

Surveillance of these patients has been very strict as it was not until only a short time ago that this approach was included in available clinical guidelines. Currently, American Urological Association guidelines (www.auanet.org) recommend this policy of conservative management for patients with low-risk and recurrent non-muscle invasive papillary bladder tumours with well-documented history of low-grade Ta tumours. This study adds the size and the number of tumours as other inclusion criteria to select patients better that could benefit from this approach.

Our patients underwent cytology and cystoscopy every 4 months over the first 2 years and ultrasound plus cytology examination thereafter. A growth in the number or size of tumours (detected by ultrasound or cystoscopy examination throughout follow-up) is the main reason to trigger active surgical treatment in our experience. The size-

increased or number-increased criterion was not an objective measure, but the patient was submitted to active treatment when he/she failed to meet the inclusion criteria for the study (more than 5 tumours, or more than 1cm in size). Despite being a group of patients with low-risk tumours, in whom the yield of urine cytology is expected to be low [10], in our series 7.1% of patients dropped out of the program owing to positive cytology test results, which is why we continue to use this test. Nevertheless, cost-effectiveness studies should be conducted to better assess the use of cytology in this context. A small number of patients (9) had tumours no longer evident during follow-up. These cases, as in other series, were considered as tumours initially misdiagnosed [6].

Admittedly, there is an alternative to TUR other than active surveillance with the use of office-based fulguration with cautery or holmium laser [11]. However, this option requires the availability of those devices at the outpatient clinic, and in addition, this may require the use of local anesthesia to alleviate pain [12].

A limitation of this study is the absence of histology in 21.4% of the AS subjects (due to loss of follow-up or patients who still remain under surveillance). Another limitation is the lack of randomization, so future randomized studies would be necessary to confirm the data presented here. Studies to specifically establish the number of resections that could be avoided in a patient throughout his/her life are also required, as this cannot be calculated with our current study design. Anxiety to delay TURBT is often present in patients who remain on surveillance; although only 1.3% of those in our series dropped out of the program at their own request, the degree of anxiety

experienced by patients regarding diagnosis and therapeutic management should be assessed with objective scales.

CONCLUSIONS

AS in a highly selected group of patients with recurrent NMIBC is feasible and oncologically safe in the long term. Patients with history of T1 should not be included in active surveillance protocols even when very small recurrences are diagnosed.

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CONCLUSIONES

CONCLUSIONES

La población española presenta una incidencia de tumor vesical más elevada que los países de su entorno. A pesar de poder tener características epidemiológicamente distintas, desconocidas hasta el momento, que justifiquen esta incidencia elevada, el comportamiento de los tumores vesicales no músculo-invasivos ha demostrado ser el mismo que el de los pacientes de su entorno.

Tras nuestro estudio, incorporamos una nueva variable como es el peso tumoral a los modelos predictivos de los que ya disponemos, que es más objetiva y reproducible que el tamaño tumoral. Será precisa una validación externa de nuestros resultados para estudiar la posible inclusión de esta variable en los modelos pronósticos utilizados en la actualidad.

Por último, establecemos la seguridad oncológica a largo plazo de un programa de vigilancia activa en tumores que por sus características clínicas y patológicas consideramos como de muy bajo riesgo, con el fin de aumentar el tiempo entre cirugías en pacientes que han de ser operados en múltiples ocasiones a lo largo de su seguimiento.

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