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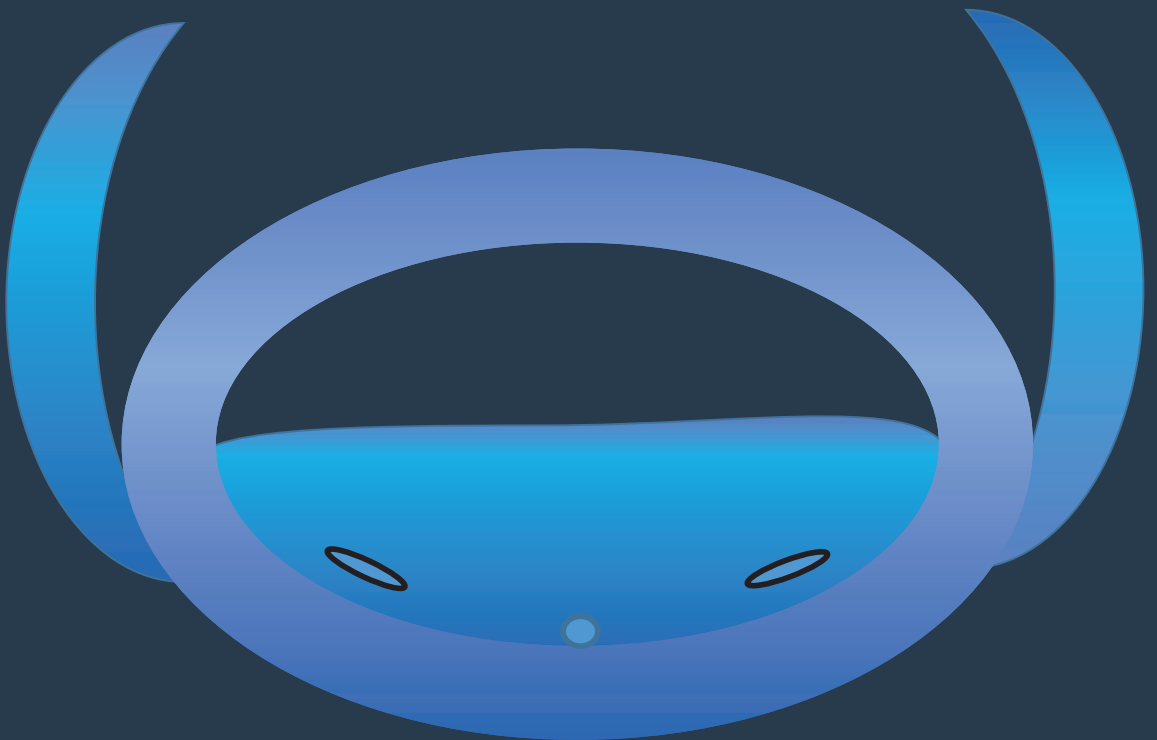
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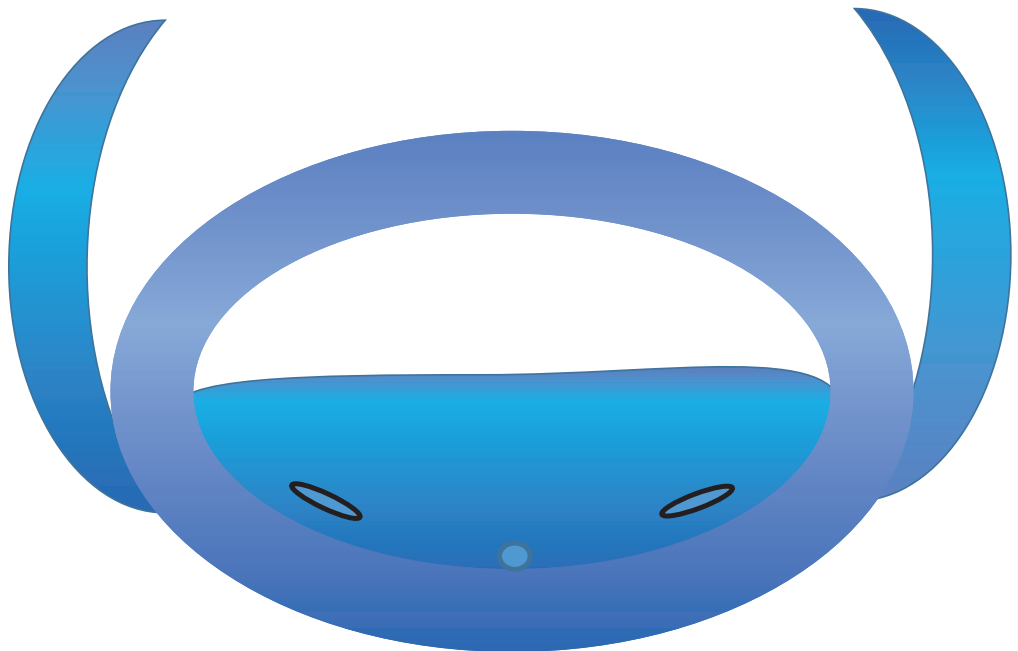
Clinical efficacy and side effects of maintenance bacillus Calmette-Guérin in the treatment of non-muscle-invasive bladder cancer

Jorg Oddens



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Clinical efficacy and side effects of maintenance bacillus Calmette-Guérin in the treatment of non-muscle-invasive bladder cancer

Klinische effectiviteit en neveneffecten van onderhoudsbehandeling met bacillus Calmette-Guérin bij de behandeling van niet-spierinvasief blaascarcinoom

Proefschrift ter verkrijging van de graad van doctor aan de Radboud Universiteit Nijmegen

op gezag van de rector magnificus,

volgens besluit van het college van decanen in het openbaar te verdedigen op

vrijdag 3 juni 2016, om 10.30 uur precies

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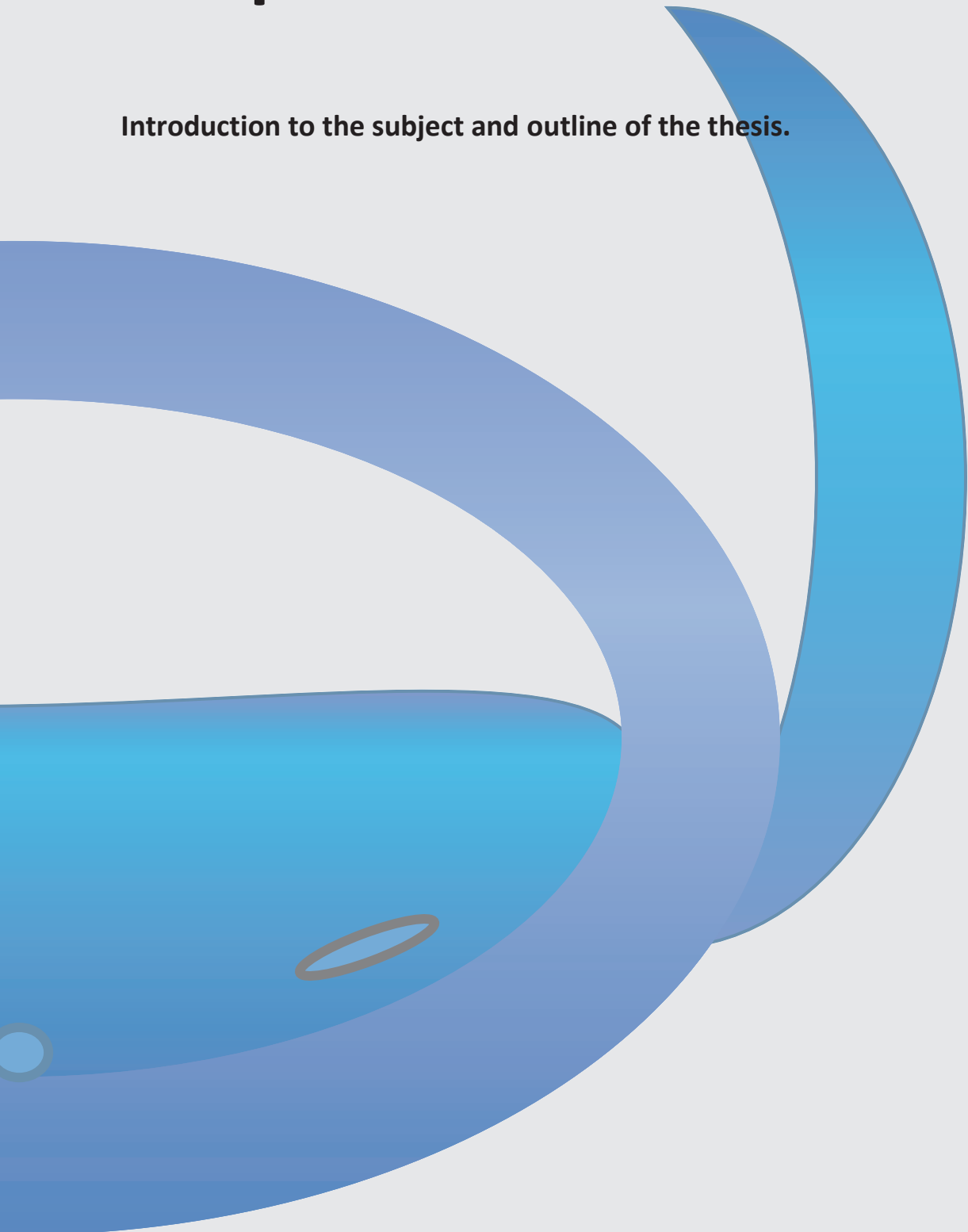
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Chapter 1

Introduction to the subject and outline of the thesis.



INTRODUCTION

Urothelial carcinoma is the 6th most common cancer in men and the 10th most common cancer in women in The Netherlands as measured in 2014 [1]. Although tumors of the urothelium can be seen in the upper urinary tract (pyelum and ureter), about 90-95% of tumors are located inside the urinary bladder.

Bladder cancer is a malignancy of the inner part of the bladder wall. It derives from the mucosa layer named urothelium that has special features to resist urine while it is stored awaiting micturition. Malignant changes often lead to thickened and fragile tissue in a papillary form. The fragility of the tissue can lead to spontaneous bleeding. Therefore, macroscopic hematuria without pain or frequency is the most common symptom.

Following the symptom of macroscopic painless hematuria the patient is referred to the urologist who will perform a cystoscopy in an outpatient clinic setting. A bladder tumor can easily be recognized in most cases. Only in case of carcinoma in situ (CIS), that gives a slightly altered aspect of the bladder mucosa appearing as a flat tumor, it can be more difficult. However, CIS usually leads to exfoliation of malignant cells that can be recognized in microscopic examination of urine. For that reason, urinary cytology is added to the diagnostic armamentarium. After a visual or cytological diagnosis, transurethral resection will be planned at the operation theatre.

With the resection of a bladder tumor we aim two goals [2]. The first is to collect tissue for pathological investigation leading to information about tumor stage and grade. The second is to remove all potentially cancerous tissue. After resection and pathological examination, tumors can be characterised by two important features: the tumor stage and the tumor grade [3, 4]. The stage is reflecting information about the anatomical behaviour of the tumor tissue: whether it is limited to the layer of tissue from which it originated or it is infiltrating surrounding tissue layers. The grade is a reflection of the histological architecture. Tumors that do not invade the detrusor muscle (Stages Tis, Ta or T1) of the urinary bladder are called non muscle invasive bladder cancer (NMIBC). In contrast, tumors that invade the detrusor muscle or beyond (T2-4) are called muscle invasive bladder cancer (MIBC) (table 1).

In the curative treatment for NMIBC it is in most cases possible to preserve the bladder and its function. In MIBC, standard curative treatment includes removing the urinary bladder as a whole, mandating an alternative for storage and passing urine, usually by creating an ileocutaneostomy or a neobladder.

Table 1. T-stadia according to TNM classification [3]

Ta	Non-invasive papillary carcinoma	Non Muscle Invasive Bladder Cancer (NMIBC)
Tis:	Non-invasive flat carcinoma (flat carcinoma in situ, or CIS)	
T1:	The tumor has grown from the layer of cells lining the bladder into the connective tissue below. It has not grown into the muscle layer of the bladder.	
T2:	The tumor has grown into the muscle layer.	Muscle Invasive Bladder Cancer (MIBC)
<i>T2a:</i>	The tumor has grown only into the inner half of the muscle layer.	
<i>T2b:</i>	The tumor has grown into the outer half of the muscle layer.	
T3	The tumor has grown through the muscle layer of the bladder and into the fatty tissue layer that surrounds it.	
<i>T3a:</i>	The spread to fatty tissue can only be seen by using a microscope.	
<i>T3b:</i>	The spread to fatty tissue is large enough to be seen on imaging tests or to be seen or felt by the surgeon.	
T4:	The tumor has spread beyond the fatty tissue and into nearby organs or structures. It may be growing into any of the following: the stroma (main tissue) of the prostate, the seminal vesicles, uterus, vagina, pelvic wall, or abdominal wall.	
<i>T4a:</i>	The tumor has spread to the stroma of the prostate (in men), or to the uterus and/or vagina (in women).	
<i>T4b</i>	The tumor has spread to the pelvic wall or the abdominal wall.	

In NMIBC, when the urinary bladder is preserved, one of the clinical issues is tumor recurrence and progression rate. One explanation for this problem is the biology of this disease: the urothelium shows tumor-changes on multiple locations and after resection of one, another site can become visible. Another explanation is an incomplete resection. Besides incomplete resection of all visible tumor, incomplete resection of non-visible tumor can occur e.g. when an invasive growth pattern exists. For these issues, several attributive steps in treatment of NMIBC are advocated:

1. Immediate postoperative chemotherapeutic instillation: within 24 hours of the TUR, a chemotherapeutic agent (mitomycin-C or epirubicin) is installed into the bladder to prevent early recurrence [5]. A major disadvantage for this strategy is the risk of

complications due to perforation of the bladder wall and subsequent leakage of the agent into surrounding tissue [6].

2. A re-resection in case of T1 and/ or G3 tumors or in case of initially recognized incomplete resection. This proved to lower recurrence and progression rates [7,8,9].
3. Adjuvant treatment.

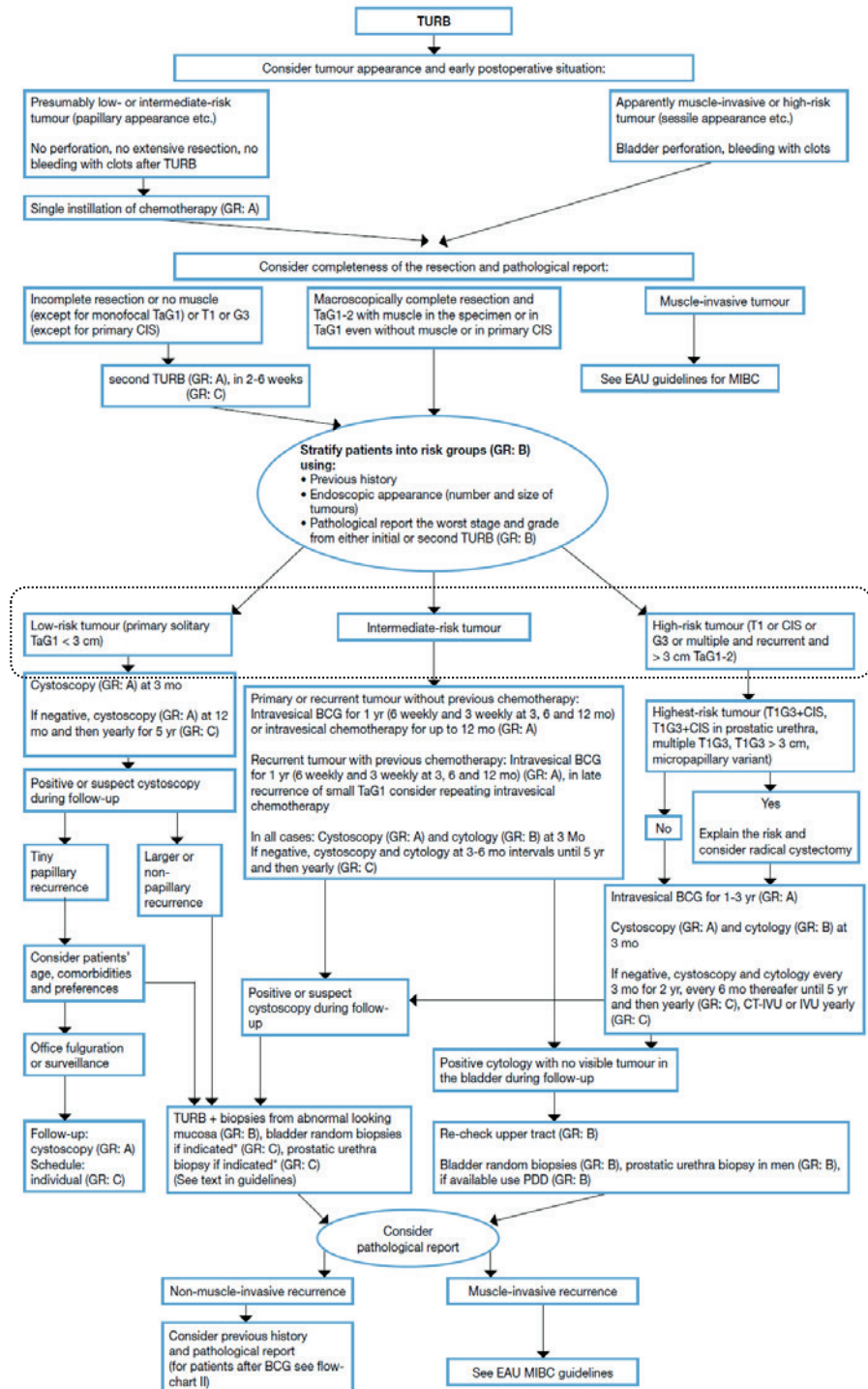
Adjuvant treatment

In NMIBC, chances of recurrence are varying from 15-61% and of progression from 0,2-17% in 1 year depending on several aspects of the disease like grade, stage, previous recurrence, amount and volume of lesions and presence of carcinoma in situ (CIS) [10]. In the EAU guidelines on NMIBC 2015, 3 risk categories are used based on this risk stratification (figure 1) [2]. For the intermediate and high risk categories, it is recommended to start adjuvant treatment using intravesical instillations with either a chemotherapeutic drug like mitomycin-C or the immune modulating drug bacillus Calmette-Guérin (BCG) with a one-year maintenance schedule. In high risk, BCG for 3 years is advised, although in a subgroup of these patients with a very high risk, early cystectomy is advocated.

History of BCG in bladder cancer treatment

BCG was originally developed as a vaccine for tuberculosis between 1908 and 1921. In 1929, the American biostatistician Raymond Pearl described a potential beneficial effect of tuberculosis in the incidence of cancer [11]. Already in 1935, Holmgren reported a study using BCG in treating stomach cancer [12]. In 1976, Morales described a beneficial effect of BCG used as bladder instillation, for which he arbitrarily used 6 weekly instillations [13]. In 1980, the first randomised controlled trial on 6 instillations of BCG was published, confirming the positive effect of BCG for bladder cancer recurrence rate [14]. The protective effect of BCG was even more pronounced when given as a maintenance treatment for a period of three years compared to the standard induction of 6 weeks. As a result of the outcome of this publication, maintenance BCG for a period of 3 years became the gold standard. Although BCG has been proven to be effective as adjuvant treatment in NMIBC, it can produce moderate to severe local and systemic side effects [15]. This has triggered the European Organization for Research and Treatment of Cancer Genito-Urinary (EORTC-GU) group to conduct two Randomized Controlled Trials (RCT) that focused on reduction of side effects while maintaining the efficacy of BCG. Trial 30911 compared maintenance BCG ± isoniazid (INH) to epirubicin. In the arms using BCG, INH, an tuberculostatic drug, was added to lower side effects. In the final analysis however, it showed not to have any beneficial effect. This has led to trial 30962 that compared the effects on both side effects and efficacy of a reduced dose and/ or a shorter maintenance period of one year with the normal dose during 3 years.

Figure 1. Risk stratification of NMIBC (Derived from EAU guidelines on NMIBC 2015) [5].



Outline of the thesis

In this thesis, we describe aspects of efficacy and side effects of BCG-treatment based on two randomized controlled trials performed by the EORTC-GU group. The final results of trial 30962 are discussed. The general results of trial 30911 were published between 2003-2010 [16,17,18,19]. Sub-analyses on the data of trial 30911 are incorporated into this thesis as is the analysis on risk factors that used data of both trials.

Part 1 will focus on the efficacy of BCG.

In **chapter 2** the results on efficacy will be discussed of EORTC trial 30962. In this trial, patients with intermediate to high risk BCG were randomized between 4 study groups that all received a certain period of a certain dose of maintenance BCG. Variation in duration (one versus three years) and amount (full versus 1/3 dose) determined the four study groups.

In **chapter 3** we focus on another important subject related to efficacy. As BCG is working by stimulation of the immune response of the patient, the aging patients may respond differently due to a decreased response capacity of their immune system, a phenomenon called immunosenescence. We investigated the role of age in the efficacy of the treatment.

Chapter 4 reflects the statistical exercise to link tumor related factors to the efficacy of BCG, based on the study results of both trials 30911 and 30962 leading to the development of a nomogram predicting the overall survival of patients treated with BCG.

Part 2 will focus on side effects of BCG.

In **chapter 5** the relation of age to the occurrence of side effects of BCG as seen in trial 30911 are explored.

In **chapter 6** the side effects as reported in trial 30962 are discussed.

We conclude in **chapter 7** with a brief summary of the most important results in regard to future developments.

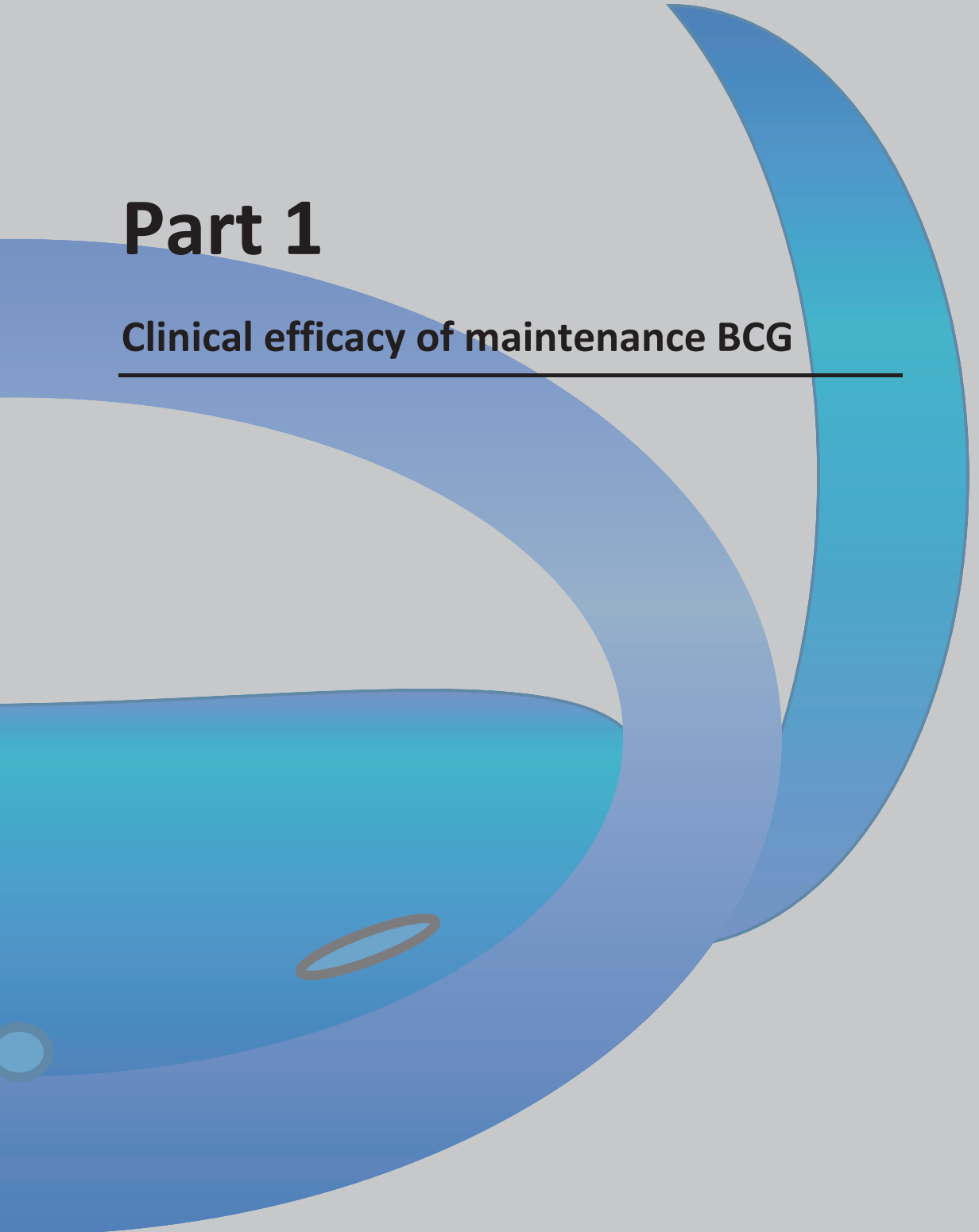
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Part 1

Clinical efficacy of maintenance BCG



Chapter 2

Final results of an EORTC GU Cancers Group randomized study of maintenance bacillus Calmette-Guérin (BCG) in intermediate and high risk Ta, T1 papillary carcinoma of the urinary bladder: One third dose versus full dose and one year versus three years of maintenance.

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ABSTRACT

Background: The optimal dose and duration of intravesical bacillus Calmette-Guérin (BCG) in the treatment of non muscle invasive bladder cancer (NMIBC) are controversial.

Objectives: To determine if one third dose (1/3D) is not inferior to full dose (FD), if 1 year (1yr) maintenance is not inferior to 3 years (3yrs) maintenance and if 1/3D and 1yr maintenance are associated with less toxicity.

Design, Setting, Participants and Intervention: After transurethral resection, intermediate and high risk NMIBC patients were randomized to one of four BCG groups: 1/3D-1 yr, 1/3D-3 yr, FD-1 yr, FD-3 yr.

Outcome Measurements and Statistical Analysis: The trial was designed as a noninferiority study with the null hypothesis of a 10% decrease in the disease-free rate at 5 yr. Times to events were estimated using cumulative incidence functions and compared using the Cox proportional hazards regression model.

Results: In an intent-to-treat analysis of 1355 patients with median follow up 7.1 yr, there were no significant differences in toxicity between 1/3D and FD. The null hypotheses of inferiority of the disease-free interval for both 1/3D and 1yr could not be rejected. 1/3D-1 yr is suboptimal compared to FD-3 yr (HR = 0.75, 95%CI: 0.59-0.94, $p = 0.01$). Intermediate risk patients treated with FD do not benefit from an additional two years of BCG. In high risk patients, 3yrs is associated with a reduction in recurrence (HR = 1.61, 95%CI: 1.13-2.30, $p = 0.009$), but only when given at FD. There were no differences in progression or survival.

Conclusions: There were no differences in toxicity between 1/3D and FD. Intermediate risk patients should be treated with FD-1 yr. In high-risk patients, FD-3 yr reduces recurrences as compared to FD-1yr, but not progressions or deaths. The benefit of the two additional years of maintenance should be weighed against its additional costs and inconveniences.

INTRODUCTION AND OBJECTIVES

After initial transurethral resection (TUR), non-muscle invasive bladder cancer (NMIBC) is characterized by a high risk of recurrence and, to a lesser extent, progression to muscle invasive disease. These risks can be quantified based on a patient's tumor characteristics using EORTC risk tables or with a simplified risk group classification [1,2]. To decrease the risk of recurrence and progression, adjuvant instillations of chemotherapy or bacillus Calmette-Guérin (BCG) are given in accordance with European Association of Urology (EAU) Guidelines [3]. In intermediate and high risk patients, the protective effects of maintenance BCG are more pronounced as compared to chemotherapy [4, 5].

The initial report by Morales et al described six weekly BCG induction instillations [6]. Afterwards, it was found that additional instillations of BCG reduced recurrences, however the optimal duration of maintenance instillations remains controversial [7-9]. Based on several meta-analyses, the EAU guidelines recommend at least 1 year of maintenance.

A major disadvantage of BCG is its toxicity, leading to interruptions and premature discontinuation of maintenance. In EORTC trial 30911, isoniazid (INH) did not reduce toxicity for patients on three years of maintenance [10]. However, toxicity was reduced when two doses of ofloxacin were given shortly after each of nine BCG instillations [11].

The Club Urológico Español de Tratamiento Oncológico (CUETO) compared the effect of a reduced dose of BCG to standard dose in intermediate and in high risk patients [12-14]. These studies, where a short schedule of < 6 mo BCG was used, suggested that one third dose (1/3D) is the minimum effective dose.

The current randomized phase 3 study (30962) was designed to investigate two strategies to decrease the toxicity of maintenance BCG without compromising its efficacy. The purpose is to show that 1/3D BCG is not inferior to full dose (FD) BCG and that 1 yr of maintenance is not inferior to 3 yr of maintenance with respect to efficacy and that 1/3D and 1 yr of maintenance are associated with less toxicity.

MATERIAL AND METHODS

Inclusion and exclusion criteria

Patients with biopsy-proven, completely resected, solitary pT1G3 or multiple pTa-T1, grade 1–3 (1973 World Health Organization [WHO] classification) urothelial carcinoma of the bladder were included. Excluded were patients with solitary tumors except T1G3, more than 10 tumors, carcinoma in situ (CIS), tumors stage T2 or higher, age > 85 yr, WHO performance status 3 or 4, previous treatment with BCG and intravesical chemotherapy during the previous 3 mo. An intravenous pyelography was performed to rule out upper tract tumors. Informed consent was obtained in accordance with the Declaration of Helsinki and/or existing national and local regulations.

Randomization and study interventions

Within 14 d after TUR, patients were randomized to one of four treatment groups:

1. One third dose BCG with 1 yr of maintenance (1/3D-1 yr): BCG was instilled once a week for 6 wk, followed by three weekly instillations at months 3, 6, and 12.
2. Full dose BCG with 1 yr of maintenance (FD-1 yr).
3. One third dose BCG with 3 yr of maintenance (1/3D-3 yr): BCG was instilled once a week for 6 wk, followed by three weekly instillations at months 3, 6, 12, 18, 24, 30 and 36, for a total of 27 instillations.
4. Full dose BCG with 3 yr of maintenance (FD-3 yr).

The OncoTICE® strain containing 5×10^8 CFU was used. Preparation of 1/3 dose was done either by dissolving 1 vial with 150ml of saline and taking 50 ml or by dissolving with 50 ml, taking 17 ml, and diluting this to 50 ml.

Patients stopped protocol treatment at the second Ta/T1 recurrence after randomization and at progression to muscle-invasive disease, appearance of CIS, carcinoma in the upper urinary tract or prostatic urethra, or distant metastases. Further treatment was at the discretion of the local investigator. Cystoscopy and urine cytology were repeated every 3 mo during the first 3 yr and every 6 mo thereafter. Recurrence of disease was established by histology.

Local (bacterial cystitis, chemical cystitis, frequency, hematuria) and systemic (fever, general malaise, lung infection, skin rash, sepsis) side effects were collected during induction and maintenance instillations according to a standardized format.

Endpoints

The primary endpoint was the duration of the disease-free interval (DFI): the time until first recurrence including progression to muscle invasive disease, distant metastases and death due to bladder cancer. Secondary endpoints included time to progression (muscle-invasive disease, distant metastases, death due to bladder cancer), duration of survival and toxicity.

Statistical considerations

The trial was designed as a non-inferiority study. Two comparisons were foreseen for each of the two null hypotheses:

- (1) The efficacy of one third dose is inferior to full dose:
 - One third versus FD BCG with 1 yr of maintenance
 - One third versus FD BCG with 3 yr of maintenance
- (2) The efficacy of one year maintenance is inferior to three years maintenance:
 - One year versus 3 yr of maintenance with 1/3 D BCG
 - One year versus 3 yr of maintenance with FD BCG

One sided non-inferiority tests at $\alpha = 0.025$ and $\beta = 0.20$ were planned for each comparison. Times to events were compared using the Wald test from a Cox proportional hazards regression model. The disease free interval and time to progression curves were estimated using cumulative incidence functions to take into account patients who died of other causes

prior to the event of interest (competing risks). Duration of survival curves were estimated using the Kaplan-Meier technique.

To reject the null hypothesis of a decrease of 10% in the 5-yr disease-free rate from 50% on the control arms (FD BCG, 3 yr of maintenance) to 40% on the experimental arms (1/3 D BCG, 1 yr of maintenance) with hazard ratio (HR) = 1.32, 414 events and 644 patients were required for each of the four comparisons. As patients were analyzed twice, a total of 1288 patients and 828 events were required, leading to 322 patients in each treatment group.

The study was reviewed in September 2011 by the EORTC Independent Data Monitoring Committee which recommended the release of the results. Since there was no interaction between the dose and duration of maintenance, the study was analyzed as a 2 x 2 factorial design, retrospectively stratifying the dose comparison by the duration of maintenance and vice versa, with a power of 92% to reject the null hypothesis of inferiority for each comparison at one sided $\alpha = 0.025$ (Table 1).

Table 1. Stratified comparison of the study arms

Study arms	1/3 dose	Full dose	<i>Dose stratified comparison of duration</i>
1 year	I	II	<i>I vs III</i>
3 years	III	IV	<i>II vs IV</i>
<i>Duration stratified comparison of dose</i>	<i>I vs II</i> + <i>III vs IV</i>		

Quality assurance

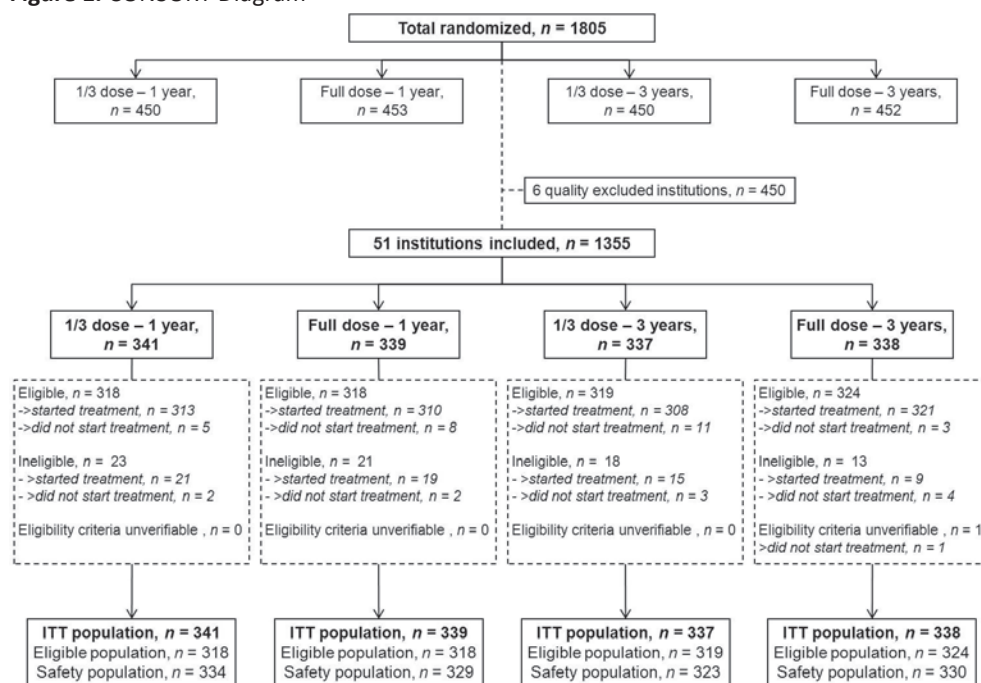
In accordance with EORTC Quality Assurance policies, central EORTC data management and quality control were supplemented by on site audits.

RESULTS

From March 1997 to April 2005, 1805 patients were centrally randomized at the EORTC HQ by 57 centers from 13 countries with stratification by site. During patient entry and prior to analysis of endpoint data, study coordinator central review (J.O. and M.B) and on site audits led to the exclusion of all data from 6 sites for non-compliance. After quality control exclusion of these 450 patients, patient entry continued until 1355 patients had been randomized: 341 to 1/3D-1 yr, 339 to FD-1 yr, 337 to 1/3D-3 yr, 338 to FD-3 yr.

A total of 75 of 1355 patients (5.5%) were ineligible, the main reasons being too long a delay between TUR and randomization and an incorrect tumor type at entry (Figure 1).

Figure 1. CONSORT Diagram



Baseline patient and tumor characteristics were generally well balanced between the 4 treatment groups (Table 2): 59% were primary tumors, 13% had a single tumor, 63% were Ta and 27% were G3. Using the simplified classification, 41% were high risk (T1 or G3) and 58% were intermediate risk, with somewhat fewer high risk patients in the 1/3D-3 yr arm.

Table 2. Patient and tumor characteristics by treatment arm

	BCG treatment arm				
	1/3 dose - 1yr (n=341)	Full dose - 1yr (n=339)	1/3 dose - 3yrs (n=337)	Full dose - 3yrs (n=338)	Total (n=1355)
	n (%)	n (%)	n (%)	n (%)	n (%)
Eligible					
No	23 (6.7)	21 (6.2)	18 (5.3)	13 (3.8)	75 (5.5)
Yes	318 (93.3)	318 (93.8)	319 (94.7)	324 (95.9)	1279 (94.4)
Unknown	0	0	0	1 (0.3)	1 (0.1)
Age (years)					
Median	68.0	67.0	69.0	67.0	68.0
Range	29.0 - 84.0	30.0 - 84.0	39.0 - 85.0	30.0 - 84.0	29.0 - 85.0
Gender					
Male	275 (80.6)	282 (83.2)	272 (80.7)	270 (79.9)	1099 (81.1)
Female	64 (18.8)	54 (15.9)	64 (19.0)	65 (19.2)	247 (18.2)
Unknown	2 (0.6)	3 (0.9)	1 (0.3)	3 (0.9)	9 (0.7)
WHO performance status					
0	281 (82.4)	278 (82.0)	273 (81.0)	287 (84.9)	1119 (82.6)
1	52 (15.2)	56 (16.5)	59 (17.5)	45 (13.3)	212 (15.6)
2	8 (2.3)	5 (1.5)	5 (1.5)	6 (1.8)	24 (1.8)
Type of bladder cancer					
Primary	208 (61.0)	212 (62.5)	195 (57.9)	178 (52.7)	793 (58.5)
Recurrent	131 (38.4)	124 (36.6)	141 (41.8)	157 (46.4)	553 (40.8)
Unknown	2 (0.6)	3 (0.9)	1 (0.3)	3 (0.9)	9 (0.7)
Number of Tumors					
Single	51 (15.0)	46 (13.6)	44 (13.1)	38 (11.2)	179 (13.2)
Multiple	286 (83.9)	291 (85.8)	291 (86.4)	295 (87.3)	1163 (85.8)
Unknown	4 (1.2)	2 (0.6)	2 (0.6)	5 (1.5)	13 (1.0)
Largest tumor diameter (mm)					
Median	15.0	15.0	15.0	12.0	15.0
Range	1.0 - 80.0	2.0 - 98.0	2.0 - 80.0	1.0 - 98.0	1.0 - 98.0
N obs	318	322	321	315	1276
T category					
pT0	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.6)	3 (0.2)
pTa	202 (59.2)	207 (61.1)	229 (68.0)	214 (63.3)	852 (62.9)
pT1	137 (40.2)	130 (38.3)	107 (31.8)	119 (35.2)	493 (36.4)
pT2	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Unknown	0 (0.0)	2 (0.6)	0 (0.0)	3 (0.9)	5 (0.4)
WHO 1973 grade					
G0	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
G1	84 (24.6)	94 (27.7)	110 (32.6)	99 (29.3)	387 (28.6)
G2	162 (47.5)	151 (44.5)	147 (43.6)	138 (40.8)	598 (44.1)
G3	95 (27.9)	91 (26.8)	78 (23.1)	97 (28.7)	361 (26.6)
Unknown	0 (0.0)	3 (0.9)	1 (0.3)	4 (1.2)	8 (0.6)

	1/3 dose - 1yr (n=341)	Full dose - 1yr (n=339)	1/3 dose - 3yrs (n=337)	Full dose - 3yrs (n=338)	Total (n=1355)
	n (%)	n (%)	n (%)	n (%)	n (%)
EORTC Recurrence Score					
≤ 9 (Intermediate Risk)	234 (68.6)	242 (71.4)	226 (67.1)	215 (63.6)	917 (67.7)
10 - 17 (High Risk)	76 (22.3)	74 (21.8)	90 (26.7)	96 (28.4)	336 (24.8)
Missing	31 (9.1)	23 (6.8)	21 (6.2)	27 (8.0)	102 (7.5)
EORTC Progression Score					
≤ 6 (Intermediate Risk)	92 (27.0)	100 (29.5)	106 (31.5)	71 (21.0)	369 (27.2)
7 – 13 (High Risk)	174 (51.0)	177 (52.2)	180 (53.4)	202 (59.8)	733 (54.1)
14 – 23 (High Risk)	44 (12.9)	39 (11.5)	30 (8.9)	38 (11.2)	151 (11.1)
Missing	31 (9.1)	23 (6.8)	21 (6.2)	27 (8.0)	102 (7.5)
Simplified Risk Group					
Intermediate risk	192 (56.3)	191 (56.3)	218 (64.7)	188 (55.6)	789 (58.2)
High risk*	149 (43.7)	146 (43.1)	119 (35.3)	146 (43.2)	560 (41.3)
Unknown	0 (0.0)	2 (0.6)	0 (0.0)	4 (1.2)	6 (0.4)

*High risk = T1 and/or G3

A total of 39 patients (3%) did not start treatment, 11 of whom were ineligible. In the remaining 1316 patients, the amount of treatment received is shown in Table 3.

Table 3. Amount of treatment received

	BCG treatment arm			
	1/3 dose - 1yr (n=341)	Full dose - 1yr (n=339)	1/3 dose - 3yrs (n=337)	Full dose - 3yrs (n=338)
	n (%)	n (%)	n (%)	n (%)
No treatment	7 (2.1)	10 (2.9)	14 (4.2)	8 (2.4)
Started treatment	334 (97.9)	329 (97.1)	323 (95.9)	330 (97.6)
Amount of treatment				
6 wk	48 (14.1)	36 (10.6)	33 (9.8)	37 (10.9)
3 mo	35 (10.3)	37 (10.9)	33 (9.8)	37 (10.9)
6 mo	44 (12.9)	43 (12.7)	46 (13.6)	37 (10.9)
12 mo	198 (58.1)	210 (61.9)	29 (8.6)	37 (10.9)
18 mo	8 (2.3)	2 (0.6)	16 (4.7)	18 (5.3)
24 mo	0	0	18 (5.3)	23 (6.8)
30 mo	1 (0.3)	1 (0.3)	24 (7.1)	19 (5.6)
36 mo	0	0	115 (34.1)	119 (35.2)
> 36 mo	0	0	9 (2.7)	3 (0.9)

Median time between TUR and first instillation was 15 d. A total of 420 of 680 patients (61.8%) randomized to 1 yr of maintenance completed 12 mo of treatment while 246 of 675 patients (36.4%) randomized to 3 yr of maintenance completed all 36 mo. A total of 103 patients (7.8%) stopped treatment due to local or systemic side effects (Table 4a, 4b): in 47 patients (7.1%) randomized to 1 yr of maintenance and 56 patients (8.6%) randomized to 3 yr of maintenance. 35 of these 56 patients (5.4%) stopped already during the first year while 21 (3.2%) stopped in the second or third year. The most frequent local side effects were bacterial and/or chemical cystitis (56.2%), hematuria (46.0%) and frequency (45.1%) whereas the most frequent systemic side effects were general malaise (15.5%) and fever (8.1%). There were no medically significant differences in toxicity between the treatment groups. Neither reducing the dose nor shortening the duration of maintenance decreased the percentage of patients who discontinued treatment due to side effects. Toxicity will be reported in more detail in a separate paper.

Tables 4a, b. Definitive stop of instillations due to side effects in patients who started treatment (per treatment group)

(a)	BCG treatment arm				
Systemic or local side effects	1/3 dose - 1yr (n=334)	Full dose - 1yr (n=329)	1/3 dose - 3yrs (n=323)	Full dose - 3yrs (n=330)	Total (n=1316)
	n (%)	n (%)	n (%)	n (%)	n (%)
Within 1st year	24 (7.2)	23 (7.0)	7 (5.3)	18 (5.5)	82 (6.2)
After the 1st year	0 (0.0)	0 (0.0)	9 (2.8)	12 (3.6)	21 (1.6)
Total	24 (7.2)	23 (7.0)	26 (8.1)	30 (9.1)	103 (7.8)

(b)	BCG intervention			
Systemic or local side effects	1/3 dose (1yr + 3yrs) (n=657)	Full dose (1yr + 3yrs) (n=659)	1 yr (1/3D + FD) (n=663)	3 yrs (1/3D + FD) (n=653)
	n (%)	n (%)	n (%)	n (%)
Within the 1st year	41 (6.2)	41 (6.2)	47 (7.1)	35 (5.4)
After the 1st year	9 (1.4)	12 (1.8)	0 (0.0)	21 (3.2)
Total	50 (7,6)	53 (8,0)	47 (7,1)	56 (8,6)

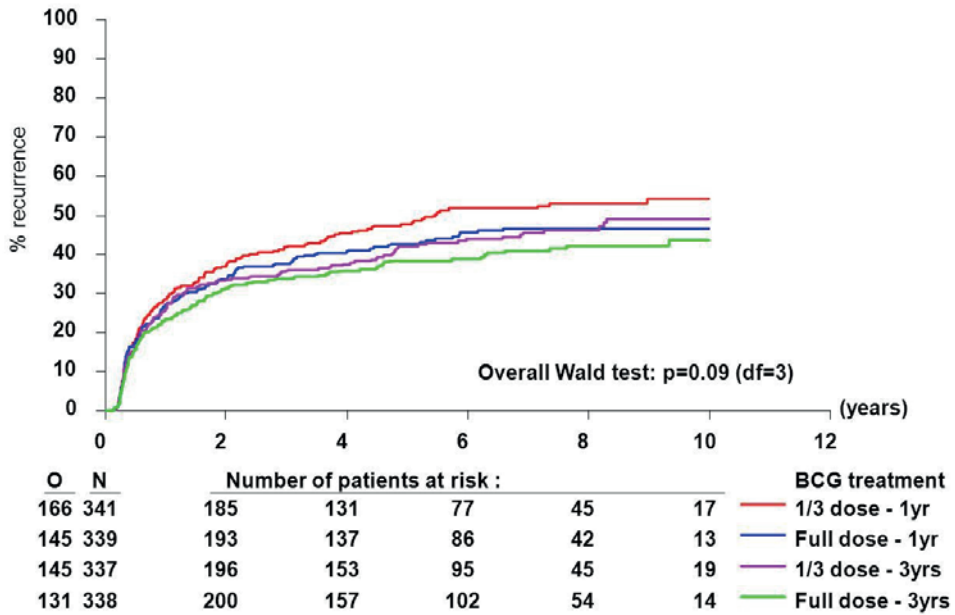
A total of 650 (49%) of 1316 patients started but did not complete their treatment. The reasons across the four treatment groups were inefficacy or recurrence in 338 (26%), toxicity in 91 (7%) and other reasons in 221 (17%).

Median follow up was 7.1 yr with a maximum of 13.5 yr. In an intent to treat analysis, 587 of 1355 patients (43.3%) recurred, including 507 (37.4%) with a Ta/T1 recurrence, 91 (6.7%) who developed CIS, 109 (8.0%) who progressed to \geq pT2 and 67 (4.9%) who developed distant metastases. 369 patients (27.2%) died, 68 (5.0%) due to bladder cancer (Table 5).

Table 5. Patient Outcome by Treatment Group

	BCG treatment arm				
	1/3 dose - 1yr (n=341)	Full dose - 1yr (n=339)	1/3 dose - 3yrs (n=337)	Full dose - 3yrs (n=338)	Total (n=1355)
	n (%)	n (%)	n (%)	n (%)	n (%)
Disease Recurrence					
No	175 (51.3)	194 (57.2)	192 (57.0)	207 (61.2)	768 (56.7)
Yes	166 (48.7)	145 (42.8)	145 (43.0)	131 (38.8)	587 (43.3)
5 Year Disease Free Rate	54.5%	58.8%	62.6%	64.2%	
Progression to \geqpT2					
No	315 (92.4)	308 (90.9)	307 (91.1)	316 (93.5)	1246 (92.0)
Yes	26 (7.6)	31 (9.1)	30 (8.9)	22 (6.5)	109 (8.0)
Presence of CIS					
No	318 (93.3)	315 (92.9)	309 (91.7)	322 (95.3)	1264 (93.3)
Yes	23 (6.7)	24 (7.1)	28 (8.3)	16 (4.7)	91 (6.7)
Distant metastases					
No	326 (95.6)	323 (95.3)	319 (94.7)	320 (94.7)	1288 (95.1)
Yes	15 (4.4)	16 (4.7)	18 (5.3)	18 (5.3)	67 (4.9)
Second primary tumor					
No	302 (88.6)	308 (90.9)	290 (86.1)	289 (85.5)	1189 (87.7)
Yes	39 (11.4)	31 (9.1)	47 (13.9)	49 (14.5)	166 (12.3)
Survival status					
Alive	258 (75.7)	251 (74.0)	236 (70.0)	241 (71.3)	986 (72.8)
Dead	83 (24.3)	88 (26.0)	101 (30.0)	97 (28.7)	369 (27.2)
<i>Bladder cancer</i>	13 (3.8)	20 (5.9)	17 (5.0)	18 (5.3)	68 (5.0)
<i>Cardiovascular</i>	29 (8.5)	34 (10.0)	39 (11.6)	32 (9.5)	134 (9.9)
<i>Other malignancy</i>	8 (2.3)	13 (3.8)	19 (5.6)	22 (6.5)	62 (4.6)
<i>Other cause</i>	18 (5.3)	13 (3.8)	18 (5.3)	13 (3.8)	62 (4.6)
<i>Cause unknown</i>	15 (4.4)	8 (2.4)	8 (2.4)	12 (3.6)	43 (3.2)

A total of 5 yr disease free (DF) rates were 54.5%, 58.8%, 62.6% and 64.2% on 1/3D-1 yr, FD-1 yr, 1/3D-3 yr and FD-3 yr, respectively (Figure 2). The pre-specified decrease of 10% in the 5yr DF rate was only observed between the patients receiving 1/3D-1yr and FD-3yrs, (HR = 0.75, 95%CI: 0.59-0.94, p = 0.01), a comparison not foreseen in the protocol.

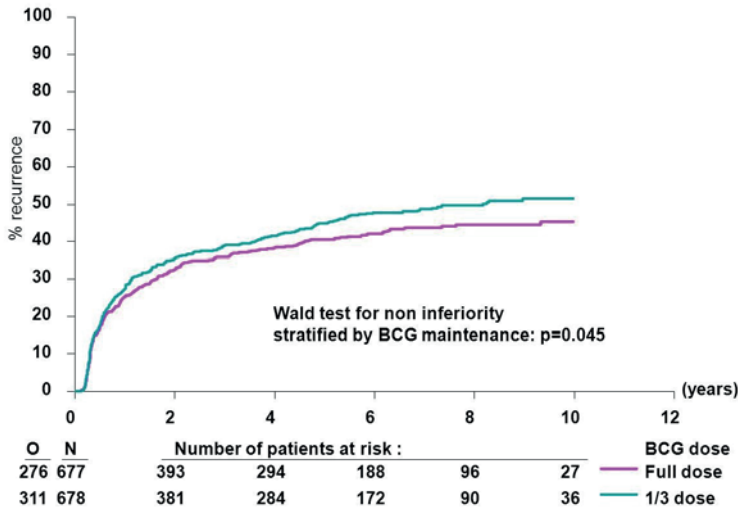
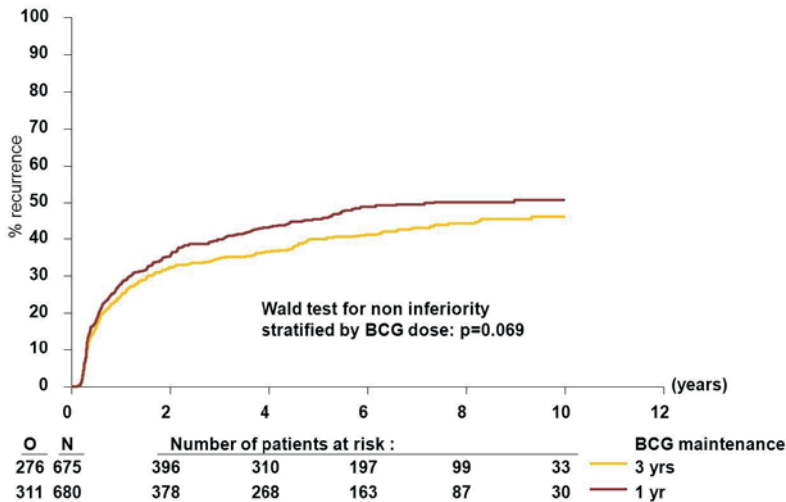
Figure 2. Disease Free Interval by Treatment Group

The 5 yr DF rate on 1/3D was 58.5% compared to 61.7% for FD. For 1 yr of maintenance, the 5 yr DF rate was 56.6% compared to 63.4% for 3 yr of maintenance (Table 6).

The null hypotheses of inferiority for duration of the DFI of 1/3D BCG (HR = 1.15, 95%CI: 0.98-1.35, $p = 0.045$, Figure 3) and 1 yr of BCG maintenance (HR = 1.17, 95%CI: 0.99-1.38, $p = 0.069$, Figure 4) could not be rejected at the one sided 0.025 level. Tests for the superiority of FD versus 1/3D ($p = 0.092$) and 3 yr versus 1 yr of maintenance ($p = 0.059$) were also not significant at the two sided 0.05 level. In patients who were still disease free at 18 mo, i.e. those patients who might benefit from continuing BCG beyond 1 yr, similar results were found.

Table 6. Patient Outcome by Treatment Type

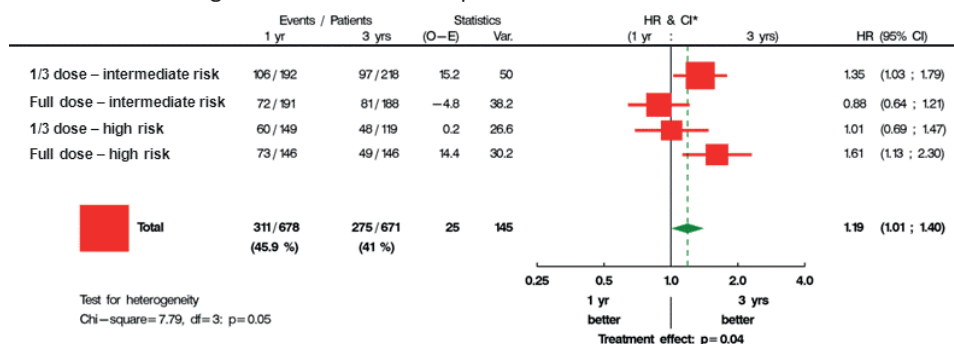
	BCG treatment			
	1/3 dose (n=678)	Full dose (n=677)	1 yr (n=680)	3 yrs (n=675)
	n (%)	n (%)	n (%)	n (%)
Recurrence				
No	367 (54.1)	401 (59.2)	369 (54.3)	399 (59.1)
Yes	311 (45.9)	276 (40.8)	311 (45.7)	276 (40.9)
5 Year Disease Free Rate	58.5%	61.7%	56.6%	63.4%
Progression to ≥pT2				
No	622 (91.7)	624 (92.2)	623 (91.6)	623 (92.3)
Yes	56 (8.3)	53 (7.8)	57 (8.4)	52 (7.7)
Presence of CIS				
No	627 (92.5)	637 (94.1)	633 (93.1)	631 (93.5)
Yes	51 (7.5)	40 (5.9)	47 (6.9)	44 (6.5)
Distant metastases				
No	645 (95.1)	643 (95.0)	649 (95.4)	639 (94.7)
Yes	33 (4.9)	34 (5.0)	31 (4.6)	36 (5.3)
Second primary tumor				
No	592 (87.3)	597 (88.2)	610 (89.7)	579 (85.8)
Yes	86 (12.7)	80 (11.8)	70 (10.3)	96 (14.2)
Survival status				
Alive	494 (72.9)	492 (72.7)	509 (74.9)	477 (70.7)
Dead	184 (27.1)	185 (27.3)	171 (25.1)	198 (29.3)
<i>Bladder cancer</i>	30 (4.4)	38 (5.6)	33 (4.9)	35 (5.2)
<i>Cardiovascular</i>	68 (10.0)	66 (9.7)	63 (9.3)	71 (10.5)
<i>Other malignancy</i>	27 (4.0)	35 (5.2)	21 (3.1)	41 (6.1)
<i>Other cause</i>	36 (5.2)	26 (3.9)	31 (4.5)	31 (4.5)
<i>Cause unknown</i>	23 (3.4)	20 (3.0)	23 (3.4)	20 (3.0)

Figure 3. Disease Free Interval: One Third Dose versus Full Dose**Figure 4.** Disease Free Interval: One Year Maintenance versus Three Years Maintenance

To take into account the imbalance in risk group distribution in the treatment groups, the two main treatment comparisons were also stratified by the simplified risk groups. Comparing 1/3D to FD BCG, the conclusions did not change. For the comparison of 1 yr to 3 yr of maintenance, the difference was significant at $p = 0.0384$ in favor of 3 yr, however the treatment effect was not homogeneous in the 4 risk by dose subgroups, $p = 0.05$ (Figure 5). In intermediate risk patients, 3 yr of maintenance was more effective than 1 yr in patients

receiving 1/3D (HR = 1.35, 95%CI: 1.03-1.79, p = 0.0318) but not in patients receiving FD BCG (HR = 0.88, 95%CI: 0.64-1.21, p = 0.4380). In high risk patients, 3 yr of maintenance was more effective than 1 yr in patients receiving FD (HR = 1.61, 95%CI: 1.13-2.30, p = 0.0087) but not in patients receiving 1/3D BCG (HR = 1.01, 95%CI: 0.69-1.47, p = 0.9716). Analyses carried out in patients who were still disease free at 18 mo yielded similar results. Comparable conclusions were obtained when stratifying by the EORTC recurrence and progression risk scores.

Figure 5. Disease Free Interval: One Year Maintenance versus Three Years Maintenance According to Dose and Risk Group



There were no significant differences between the treatment groups for the time to progression (Figure 6) or overall duration of survival (Figure 7).

Figure 6. Time to Progression by Treatment Group

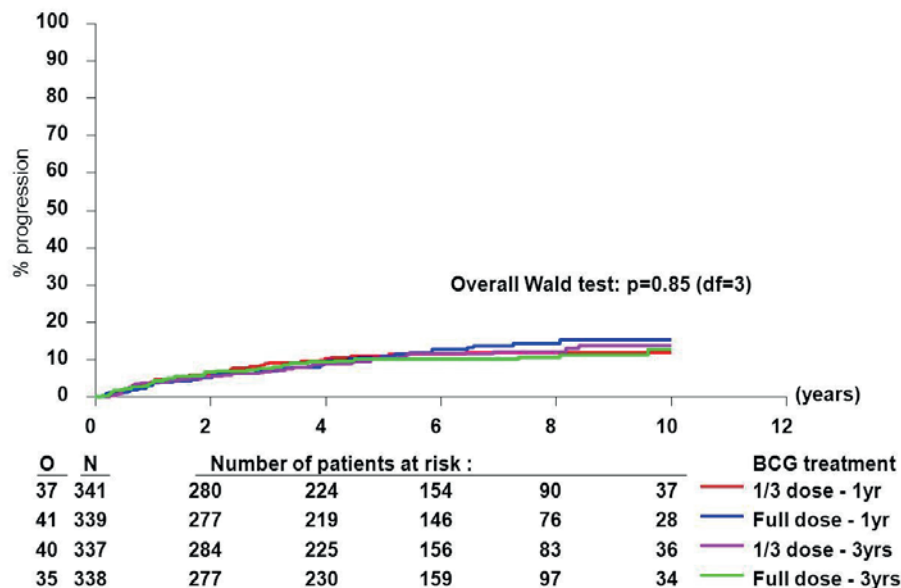
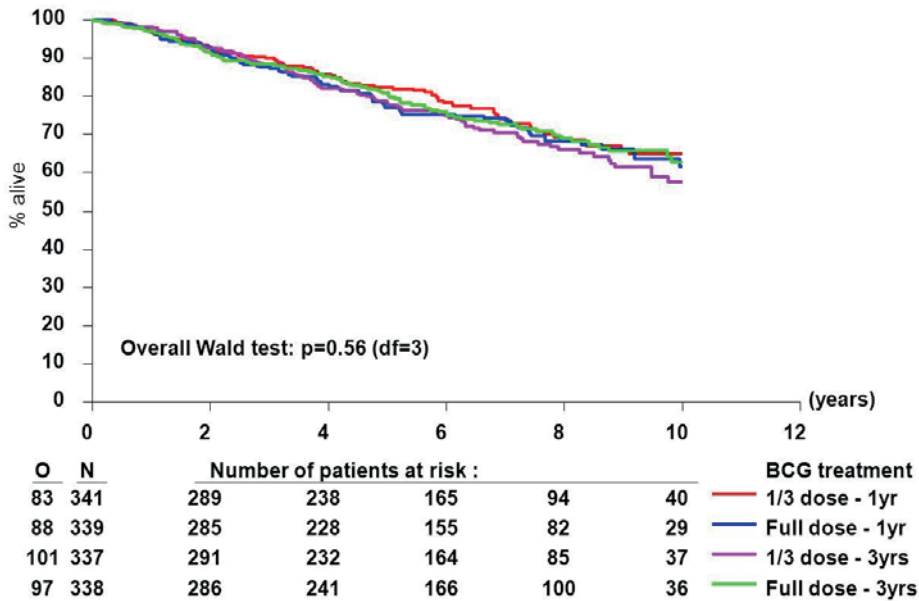


Figure 7. Duration of Survival by Treatment Group

DISCUSSION

The aim of this study was to prove that decreasing the dose of BCG from FD to 1/3 D and/or shortening maintenance from 3 yr to 1yr to reduce toxicity would not compromise treatment efficacy.

CUETO published several studies with a reduction of BCG to 1/3 D and one-sixth dose (1/6 D). In one report, CUETO claimed the efficacy of 1/3 D was comparable to FD [13], however their trial was not designed as a non-inferiority study [15]. In another study, intermediate risk patients were randomized between 1/3 D and 1/6 D BCG and 30 mg of mitomycin-C (MMC) [14]. They concluded that 1/6 D is suboptimal as compared to 1/3 D and more toxic as compared to MMC. Their maximum treatment duration was 5 months whereas in the current study, where there were no significant differences in toxicity between 1/3D and FD BCG, the minimum treatment duration was 1 yr.

In our study, the null hypotheses of a decrease of 10% in the disease free rate at 5 yr could not be rejected for either one third dose or 1 yr maintenance. Testing for superiority, the differences in the disease free rate were likewise not significant for either the dose or duration of maintenance. The observed difference at 5 yr reached 10% only between 1 yr-1/3D and 3 yr-FD, $p = 0.01$. One third dose during 1 y is insufficient treatment.

In intermediate risk patients, 3 yr of maintenance is not more effective than 1 yr when full dose is given. In high risk patients, 3 yr of maintenance reduces recurrences when FD is given ($p = 0.009$), but not when 1/3D is applied ($p = 0.97$).

Although the median follow-up is 7.1 yr, the recurrence rate was lower than expected. Nevertheless, analysis of the study based on a 2 x 2 factorial design provided a power of 92% to reject the null hypothesis of treatment inferiority. The lower than expected recurrence rate might be explained by improvements in TUR technique. The TUR procedure was not described in the protocol, but the introduction of better endoscopes and more meticulous TUR techniques during the 8 years of patient entry may have led to a reduced recurrence rate [16]. After the start of patient entry, the important role of a restaging TUR also emerged [17,18], but it is unknown how many patients had a re-TUR. The value of an immediate post-operative instillation was not known yet.

The current risk group definitions and 1999/2004 grading systems did not exist when the study was designed. However, because intermediate risk patients might not need as aggressive treatment as high risk patients [3], separate analyses were carried out in intermediate and high risk (T1 and/or G3) patients showing that two additional years of maintenance with FD BCG reduced recurrences in high risk patients but not in intermediate risk patients.

CONCLUSION

This is the largest study on the toxicity and efficacy of BCG dose reduction and duration of maintenance. There were no significant differences in toxicity between 1/3D and FD BCG. Based on the primary endpoint of disease free interval, 1/3D with 1 yr of maintenance is suboptimal compared to standard full dose during 3 yr. It is recommended to treat intermediate risk patients with FD for 1 yr as there is no further improvement in outcome by continuing treatment to 3 yr.

In high risk patients, FD-3 yr BCG reduces recurrences as compared to FD-1 yr, however there were no long term differences in progression or survival. The benefit of the two additional years of maintenance should thus be weighed against its additional costs, side effects and inconveniences.

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Chapter 3

The effect of age on the efficacy of maintenance bacillus Calmette-Guérin relative to maintenance epirubicin in patients with stage Ta T1 urothelial bladder cancer: Results from EORTC GU Group study 30911.

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ABSTRACT

Background: Although maintenance Bacillus-Calmette-Guérin (BCG) is the recommended treatment in high-risk non-muscle-invasive bladder cancer (BC), its efficacy in older patients is controversial.

Objectives: To determine the effect of age on prognosis and treatment outcome in patients with stage Ta-T1 BC treated with maintenance BCG.

Design, Setting, Participants, Intervention: 957 patients with intermediate or high risk Ta-T1 (without CIS) BC were randomized in EORTC trial 30911 comparing 6 weekly instillations of epirubicin, BCG and BCG plus isoniazid followed by 3 weekly maintenance instillations during 3 years.

Outcome Measurements, Statistical Analysis: Cox multivariate proportional hazards regression models were used to assess the relative importance of age for recurrence, progression, overall and BC specific survival with adjustment for EORTC risk scores.

Results: 822 eligible patients were included: 546 patients in the BCG +/- INH arms and 276 in the epirubicin arm. In patients treated with BCG +/- INH, 34.1% were older than 70 years and 3.7% were older than 80. With a median follow up of 9.2 years, patients older than 70 had a shorter time to progression ($p = 0.028$), overall ($p < 0.001$) and BC specific survival ($p = 0.049$) after adjustment for EORTC risk scores in the multivariate analysis. The time to recurrence was similar compared to the younger patients. BCG was more effective than epirubicin for all four endpoints considered and there was no evidence that BCG was any less effective as compared to epirubicin in patients older than 70 years.

Conclusions: In intermediate and high risk Ta T1 urothelial bladder cancer patients treated with BCG, patients older than 70 years have a worse long term prognosis, however BCG is more effective than epirubicin independent of patient age.

INTRODUCTION

The challenge in the treatment of non-muscle invasive bladder cancer (NMIBC) is to retain the bladder and its function for as long as possible, accepting to a certain extent the risk of recurrence while minimizing the probability of progression to muscle invasive disease. To quantify these risks, the EORTC risk tables can be used [1,2]. After TURBT, preferably followed by an immediate postoperative instillation and pathological confirmation of the stage and grade of the disease, adjuvant intravesical instillations are recommended in the intermediate and high risk groups, with BCG being the treatment of choice in high risk patients [2].

BCG with maintenance is more effective than chemotherapeutic agents such as mitomycin C and epirubicin in preventing recurrences, however its superiority over mitomycin C in preventing progression could not be proven in an individual patient data meta-analysis [3-7]. In spite of the superiority of maintenance BCG with regard to the reduction of the recurrence rate, the increased incidence and potential severity of BCG toxicity compared to chemotherapeutic agents prevents it from being recommended in all patients with NMIBC [2, 8, 9]. Therefore, in daily practice, it is only in high and possibly in intermediate risk patients that the benefit of BCG therapy is considered to outweigh the risk of toxicity.

The working mechanism of BCG in the treatment of bladder cancer is still not completely clarified. Influx of immune cells into the bladder wall, such as polymorphonuclear neutrophil granulocytes (PMN), T-helper cells, T-cells and Natural Killer (NK) cells is seen. These immunological responses also lead to an elevation of cytokines in urine [10].

The part of the massive immunogenic cascade triggered by BCG which is responsible for its anti-tumor effect has not been unraveled completely. What we do know is that the effectiveness of the treatment is related to a quantitative response of the immune system. In patients treated with BCG, the clinical response depends, for example, on the increase of IL-2 measured in urine samples during the induction course [11,12].

It is therefore likely that individual differences in immunological response contribute to differences in a patient's response to BCG. In line with this assumption, it can be hypothesized that factors contributing to a deterioration of one's immune system may negatively influence treatment outcome. The most obvious factor in this regard is patient age.

The capacity to generate an adequate immune response decreases with age. This phenomenon is called immunosenescence. Already in the 1970's it was shown that immune responses, especially T-cell mediated responses, were significantly depressed in healthy people above 60 years of age compared to a control group younger than 25 years of age [13]. In more recent studies focusing on the beneficial effects of vaccination programs, age is a challenging problem: older patients have a higher risk of dying of infectious disease but also have a worse immunological response to the vaccine resulting in a lower protection against the infection [14]. This raises the question of what influence age has in the response of NMIBC patients treated with BCG, in a disease that is predominantly present in older people. Approximately 65% of bladder cancer patients in the SEER-database were over 65 years of age [15].

In order to study the effect of age on the prognosis and treatment outcome in patients with stage Ta T1 urothelial bladder cancer treated with maintenance BCG, we used the database of EORTC trial 30911 which compared 6 weekly instillations of epirubicin, BCG and BCG plus isoniazid (INH) followed by maintenance instillations during 36 months [7,8]. This allowed us not only to determine the variability in outcome related to age in BCG-treated patients but also to compare the outcome with BCG to the results obtained with epirubicin in both the younger and older patients.

MATERIAL & METHODS

From January 1992 to February 1997, 957 patients with intermediate or high risk stage Ta T1 urothelial bladder cancer were randomized in EORTC GU Group trial 30911. In this European multicenter study, patients with single or multiple, primary or recurrent, completely resectable stages Ta to T1, grades 1 to 3, histological proven urothelial bladder cancer were included. Exclusion criteria were a primary solitary tumor, muscle invasive tumor or carcinoma in situ, patient age older than 85 years, a WHO performance status 3 or 4, previous treatment with doxorubicin, epirubicin or BCG and intravesical treatment during the previous 3 months. Tumors were classified according to the 1992 TNM classification of the International Union against Cancer [16].

Within 24 hours after TUR, before receiving the definitive histology report, patients were randomized to one of 3 adjuvant treatment arms: epirubicin weekly for 6 consecutive weeks starting within 24 hours after transurethral resection or BCG +/- INH weekly for 6 consecutive weeks starting 7 to 15 days after transurethral resection. In all groups, the initial 6 instillations were followed by 3 weekly instillations at months 3, 6, 12, 18, 24, 30 and 36. Cytology and cystoscopy were performed every 3 months during the first 3 years and every 6 months thereafter. In case of a suspected recurrence, pathological confirmation by a TUR was mandatory. The primary endpoint was the time to first bladder recurrence with secondary endpoints of time to muscle-invasive disease, time to distant metastases, time to progression (muscle invasion or distant metastases), overall duration of survival, and time to death due to bladder cancer. The efficacy results have been previously published [7,8].

In order to determine the prognostic importance of age in patients treated with BCG and to compare the outcome with BCG to the results obtained with epirubicin in both the younger and older patients, Cox univariate and multivariate proportional hazards regression models were fit with endpoints time to recurrence, time to progression (muscle invasive or metastatic disease), and overall and disease specific mortality. Based on the literature [17,18], two age groups were defined: younger than or equal to 70 years and older than 70 years of age. The effect of age as a continuous variable was also assessed. In the multivariate analyses, the effect of age was adjusted for the EORTC recurrence (0-17) and recoded progression (0-6, 7-13, 14-23) scores [1]. Recoded progression scores were used due to the smaller number of patients with progression and death due to bladder cancer. Times to event were estimated using cumulative incidence curves in order to take into account patients who may have died

before the event of interest (competing risk) except for overall survival which was estimated using Kaplan-Meier curves.

RESULTS

Because randomization took place before histology was known, 120 of the 957 randomized patients were ineligible. In the 837 eligible patients, data on age were lacking in 15 patients, resulting in 822 patients who are included in the current analysis: 546 patients in the BCG +/- INH arms and 276 patients in the epirubicin arm which was used as a reference group.

The distribution of age along with other patient characteristics is provided in Table 1. In the 546 patients treated with maintenance BCG +/- INH, 360 (65.9%) were less than or equal to 70 years of age, while 34.1% were older than 70 years. Only 20 patients (3.7%) were older than 80 years. Table 2 reflects the distribution of age according to the EORTC recurrence and progression scores in BCG patients and Appendix-table 1 provides patient outcome according to treatment group for the various endpoints.

Table 3 provides the results of the univariate and the EORTC recurrence and progression score adjusted analyses of age (both dichotomized and as a continuous variable) in BCG patients.

Based on a median duration of follow up of 9.2 years, there wasn't a significant effect of age on time to recurrence in patients receiving BCG (Table 3 and Figure 1). However, in both the univariate and multivariate analyses, BCG patients older than 70 years had a significantly shorter time to progression (Table 3 and Figure 2), overall survival (Table 3 and Appendix-Figure 1) and bladder cancer specific survival (Table 3 and Figure 3) than BCG patients less than or equal to 70 years. When analyzed as a continuous variable, older patients also had a shorter time to progression and overall survival in both the univariate and adjusted analyses. For the four endpoints considered above, forest plots in Figures 4a – 4d show the benefit of BCG as compared to epirubicin in the two age groups, with similar reductions in the event rate on BCG in both age groups for all 4 endpoints.

Table 1. Distribution of Patient Characteristics according to Treatment

	Treatment		Total
	BCG +/- INH (n=546) n (%)	Epirubicin (n=276) n (%)	(n=822) n (%)
Age			
≤ 60 Years	146 (26.7)	74 (26.8)	220 (26.8)
61-70 Years	214 (39.2)	100 (36.2)	314 (38.2)
71-80 Years	166 (30.4)	90 (32.6)	256 (31.1)
> 80 Years	20 (3.7)	12 (4.3)	32 (3.9)
Sex			
Male	429 (78.6)	223 (80.8)	652 (79.3)
Female	117 (21.4)	53 (19.2)	170 (20.7)
Prior Recurrence Rate			
Primary	238 (43.6)	127 (46.0)	365 (44.4)
Recurrent, ≤ 1 rec/yr	145 (26.6)	61 (22.1)	206 (25.1)
Recurrent, > 1 rec/yr	149 (27.3)	85 (30.8)	234 (28.5)
Unknown	14 (2.6)	3 (1.1)	17 (2.1)
Largest Tumor Diameter			
≤ 1 cm	265 (48.5)	132 (47.8)	397 (48.3)
≤ 3 cm	210 (38.5)	110 (39.9)	320 (38.9)
> 3 cm	49 (9.0)	19 (6.9)	68 (8.3)
Unknown	22 (4.0)	15 (5.4)	37 (4.5)
Number of Tumors			
1	86 (15.8)	35 (12.7)	121 (14.7)
2-7	395 (72.3)	212 (76.8)	607 (73.8)
≥ 8	59 (10.8)	22 (8.0)	81 (9.9)
Unknown	6 (1.1)	7 (2.5)	13 (1.6)
T Category			
Ta	342 (62.6)	179 (64.9)	521 (63.4)
T1	203 (37.2)	95 (34.4)	298 (36.3)
Unknown	1 (0.2)	2 (0.7)	3 (0.4)
Grade (1973 WHO)			
G1	204 (37.4)	108 (39.1)	312 (38.0)
G2	268 (49.1)	133 (48.2)	401 (48.8)
G3	71 (13.0)	31 (11.2)	102 (12.4)
Unknown	3 (0.5)	4 (1.4)	7 (0.9)
Recurrence Score			
0-4	150 (27.5)	74 (26.8)	224 (27.3)
5-9	309 (56.6)	158 (57.2)	467 (56.8)
10-17	42 (7.7)	20 (7.2)	62 (7.5)
Unknown	45 (8.2)	24 (8.7)	69 (8.4)
Progression Score			
0-6	314 (57.5)	164 (59.4)	478 (58.2)
7-13	180 (33.0)	83 (30.1)	263 (32.0)
14-23	20 (3.7)	8 (2.9)	28 (3.4)
Unknown	32 (5.9)	21 (7.6)	53 (6.4)

Table 2. Distribution of Age according to EORTC Recurrence and Progression Scores in BCG Patients

	Age				Total (n=546)
	≤ 60 yr (n=146)	61-70 yr (n=214)	71-80 yr (n=166)	> 80 yr (n=20)	
	n (%)	n (%)	n (%)	n (%)	n (%)
Recurrence Score					
0-4	42 (28.8)	72 (33.6)	31 (18.7)	5 (25.0)	150 (27.5)
5-9	82 (56.2)	107 (50.0)	106 (63.9)	14 (70.0)	309 (56.6)
10-17	8 (5.5)	19 (8.9)	14 (8.4)	1 (5.0)	42 (7.7)
Unknown	14 (9.6)	16 (7.5)	15 (9.0)	0 (0.0)	45 (8.2)
Progression Score					
0-6	87 (59.6)	130 (60.7)	86 (51.8)	11 (55.0)	314 (57.5)
7-13	44 (30.1)	67 (31.3)	61 (36.7)	8 (40.0)	180 (33.0)
14-23	4 (2.7)	8 (3.7)	7 (4.2)	1 (5.0)	20 (3.7)
Unknown	11 (7.5)	9 (4.2)	12 (7.2)	0 (0.0)	32 (5.9)

Table 3. Univariate and EORTC Risk Score Adjusted Effect of Age in BCG Patients

Univariate	Recurrence		Progression		Overall Survival		Death Bladder Cancer	
	HR [95% CI]	<i>p</i> -value	HR [95% CI]	<i>p</i> -value	HR [95% CI]	<i>p</i> -value	HR [95% CI]	<i>p</i> -value
Age (years)								
≤70	1	0.11	1	0.019	1	< 0.001	1	0.050
>70	1.26 [0.95-1.66]		1.92 [1.10-3.34]		2.57 [1.90-3.48]		2.40 [0.97-5.91]	
Age (Continuous)	1.00 [0.99-1.02]	0.88	1.03 [1.00-1.07]	0.033	1.08 [1.06-1.10]	< 0.001	1.03 [0.98-1.08]	0.302
Multivariate	Recurrence*		Progression**		Overall Survival**		Death Bladder Cancer**	
	HR [95% CI]	<i>p</i> -value	HR [95% CI]	<i>p</i> -value	HR [95% CI]	<i>p</i> -value	HR [95% CI]	<i>p</i> -value
Age (years)								
≤70	1	0.29	1	0.028	1	< 0.001	1	0.049
>70	1.17 [0.88-1.57]		1.89 [1.07-3.34]		2.55 [1.86-3.48]		2.55 [1.00-6.49]	
Age (Continuous)	1.00 [0.98-1.01]	0.64	1.03 [1.00-1.06]	0.047	1.08 [1.06-1.10]	< 0.001	1.03 [0.98-1.08]	0.312

* Adjusted for EORTC recurrence score (0 – 17)

**Adjusted for recoded EORTC progression score (0-6, 7-13, 14-23)

Figure 1. Distribution of Patient Characteristics according to treatment.

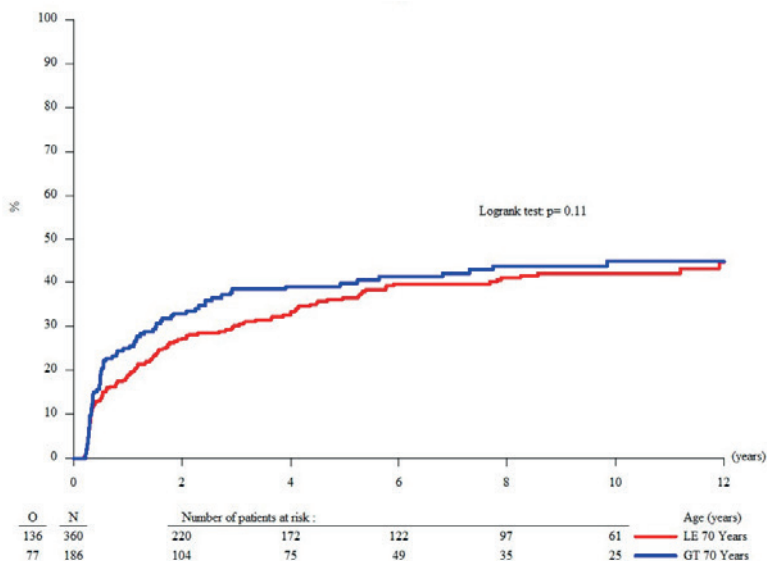


Figure 2. Time to progression in BCG patients by age group (LE= equal or younger than 70, GT= older than 70).

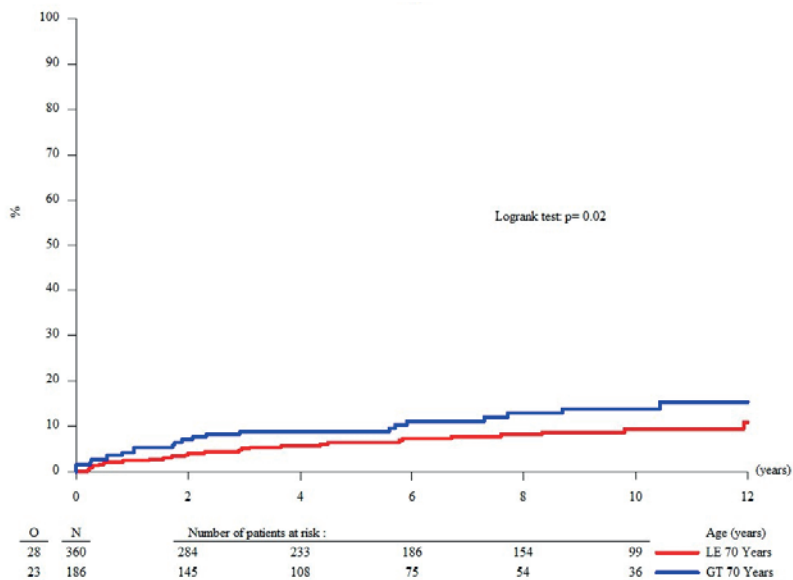


Figure 3. Bladder cancer specific mortality of BCG patients by age group (LE= equal or younger than 70, GT= older than 70).

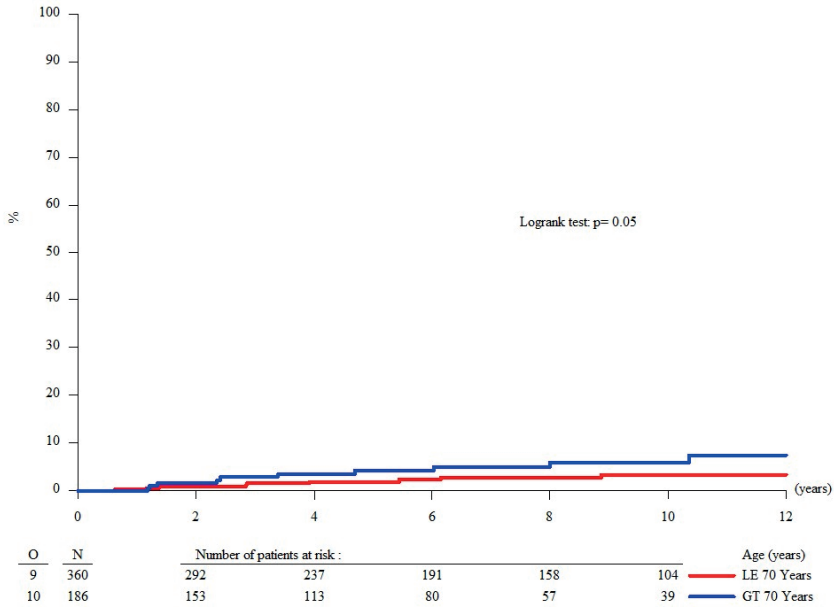


Figure 4a. Time to First Recurrence. (LE= equal or younger than 70, GT= older than 70).

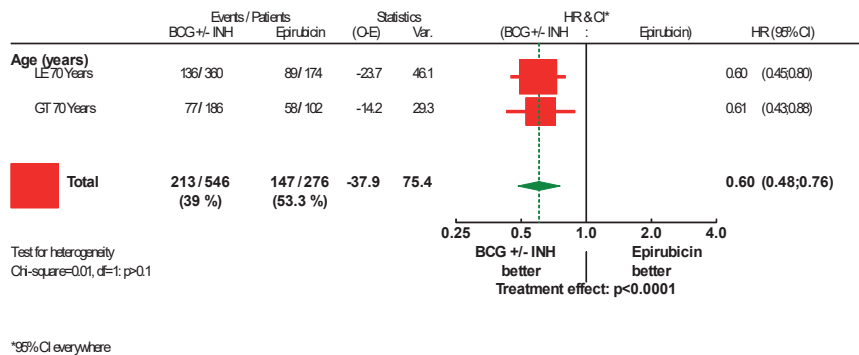


Figure 4b. Time to Progression. (LE= equal or younger than 70, GT= older than 70).

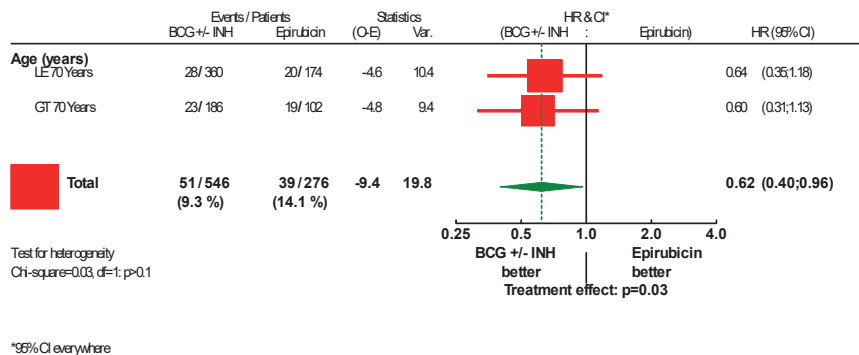


Figure 4c. Duration of Survival. (LE= equal or younger than 70, GT= older than 70).

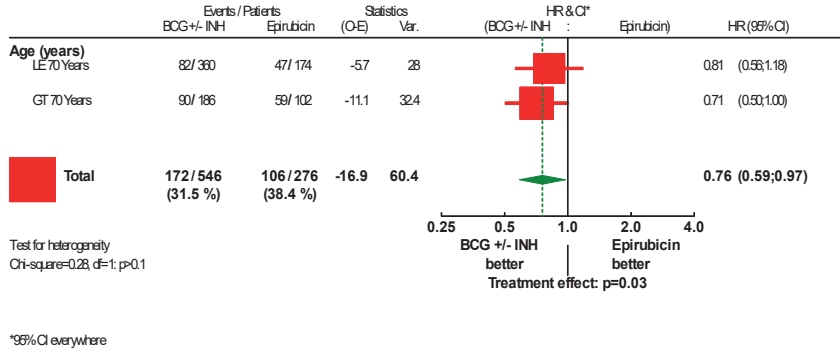
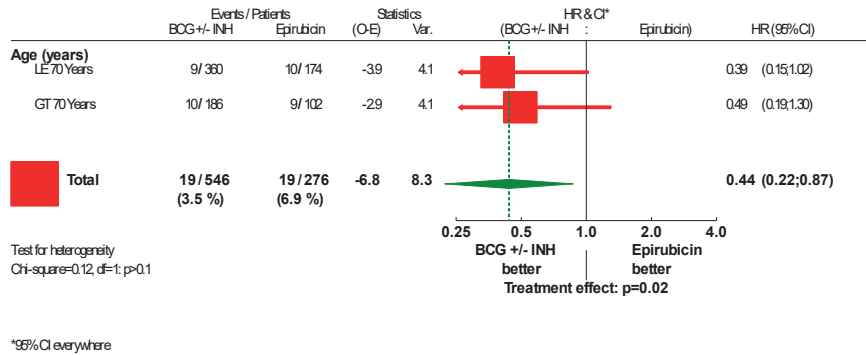


Figure 4d. Bladder cancer specific mortality. (LE= equal or younger than 70, GT= older than 70).



DISCUSSION

The most effective adjuvant treatment for decreasing the recurrence rate in intermediate and high risk NMIBC patients is immunotherapy by BCG instillations in a maintenance scheme.

On the basis of cytokine studies on IL-2 and IL-10 in urine samples that showed individual differences in immune responses related to different treatment outcome, one could hypothesize that, when the immune system is less active, the outcome of BCG treatment might be worse [11,19]. The immune system deteriorates as one grows older, a phenomenon known as immunosenescence [13,14]. Hence, one could expect that the response to BCG will in general decline with age.

In the evaluation of a phase II trial in which 1106 patients were treated with BCG combined with IFN alpha in a maintenance scheme of 1 year, age above 80 years compared to patients 61 - 70 years was indeed an independent negative predictor of cancer-free survival with an adjusted HR of 1.564 (1.065–2.296), $p = 0.02$ [17].

Two reports on age and BCG induction only in high risk patients also showed that age was a prognostic factor for treatment outcome. In one of these, age above 70 years was a prognostic factor with regards to recurrence [18]. In the second report, advanced age (≥ 75 years) was associated with a higher progression rate [20].

In the current study, age greater than 70 years was also found to be a negative factor for the prognosis of patients treated with maintenance BCG with respect to time to progression, overall and bladder cancer specific survival but not for time to recurrence. When coded as a continuous variable, older patients also had a worse prognosis for both time to progression and overall survival. A limitation of our study, however, is the upper age limit of 85 years which has reduced the number of patients in the older age group.

CUETO, which used a scheme of 12 BCG instillations during 5 months, as compared to the current report involving a true maintenance scheme of 36 instillations during 3 years, found age above 60 years to be an independent prognostic factor for progression, $p = 0.052$ [21]. One of the main findings in the current report is that despite a worse outcome in patients more than 70 years of age, BCG is still more effective than epirubicin even in this older age group.

Despite the negative prognostic effect of age, why is BCG still more effective than epirubicin even in the older patients? It is possible that the immunological response to full dose BCG may be much stronger than necessary for an adequate anti-tumor response, allowing some older patients to retain a less intense but still therapeutic response. This may explain why a reduced dose of BCG can still be effective, although recent data suggest that full dose BCG is more effective than one third or one quarter dose BCG [22, 23]. But if immunosenescence is the reason for the decreased efficacy of BCG, it could be that older patients may also have a poorer response to epirubicin or chemotherapeutics in general, so that BCG still maintains its advantage in efficacy compared to epirubicin. To our knowledge, no studies assessing the efficacy of chemotherapeutic instillations according to age have been published [24].

Besides the upper age limit of 85 years, there are several other limitations to this study. Patients were entered from 1992 until 1997 so not all patients were treated in accordance with current guidelines. High risk patients did not have a re-TURB and 32% of the high risk patients received epirubicin. No patients had a fluorescence cystoscopy. However, BCG maintained its superiority to epirubicin even in the intermediate risk patients [7] whose treatment matches the recommendations in current guidelines. The results of this study are thus expected to be valid in current day practice.

CONCLUSIONS

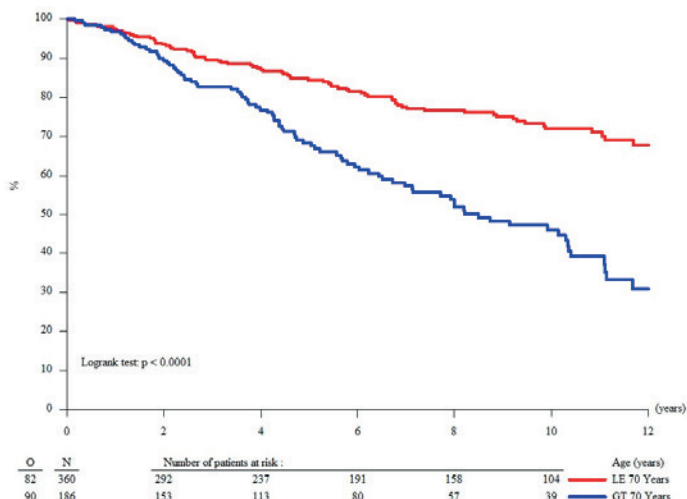
In intermediate and high risk stage Ta T1 urothelial bladder cancer patients who receive BCG, BCG is less effective in patients older than 70 years of age in terms of time to progression, overall and bladder cancer specific survival. The time to recurrence did not depend on age. However, BCG is still more effective than epirubicin even in this older age group for the endpoints considered.

APPENDIX

Appendix-table 1. Treatment Outcome.

	Treatment		Total (n=822) n (%)
	BCG +/- INH (n=546) n (%)	Epirubicin (n=276) n (%)	
	Recurrence		
No	333 (61.0)	129 (46.7)	462 (56.2)
Yes	213 (39.0)	147 (53.3)	360 (43.8)
Muscle Invasion			
No	504 (92.3)	252 (91.3)	756 (92.0)
Yes	42 (7.7)	24 (8.7)	66 (8.0)
Distant Metastases			
No	518 (94.9)	252 (91.3)	770 (93.7)
Yes	28 (5.1)	24 (8.7)	52 (6.3)
Progression (Muscle Invasion or Metastases)			
No	495 (90.7)	237 (85.9)	732 (89.1)
Yes	51 (9.3)	39 (14.1)	90 (10.9)
Cause of Death			
Alive	374 (68.5)	170 (61.6)	544 (66.2)
Bladder Cancer	19 (3.5)	19 (6.9)	38 (4.6)
Other/Unknown	153 (28.0)	87 (31.5)	240 (29.2)

Appendix-figure 1. Overall survival in BCG patients by age group (LE= equal or younger than 70, GT= older than 70).



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Chapter 4

EORTC nomograms and risk groups for predicting recurrence, progression, disease specific and overall survival in non-muscle invasive stage Ta T1 urothelial bladder cancer patients treated with 1 to 3 years of maintenance bacillus Calmette-Guérin.

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ABSTRACT

Background: There are no prognostic factor publications in stage Ta-T1 non-muscle invasive bladder cancer (NMIBC) treated with 1 to 3 years of maintenance Bacillus Calmette-Guérin (BCG).

Objectives: To determine prognostic factors in NMIBC patients treated with 1 to 3 years of BCG after transurethral resection of the bladder (TURB), to derive nomograms and risk groups and to identify high risk patients who should be considered for early cystectomy.

Design, Setting and Participants: Data for 1812 patients were merged from two European Organization for Research and Treatment of Cancer randomized phase 3 trials in intermediate and high risk NMIBC.

Interventions: Patients received 1-3 years of maintenance BCG after TURB and induction BCG.

Outcome measurements and statistical analysis: Prognostic factors for risk of early recurrence and times to late recurrence, progression and death were identified in a training data set using multivariable models and applied to a validation dataset.

Results and Limitations: With a median follow up of 7.4 years, 762 patients recurred, 173 progressed and 520 died, 83 due to bladder cancer (BCa). Statistically significant prognostic factors identified by multivariable analyses were prior recurrence rate and number of tumors for recurrence, and tumor stage and grade for progression and death due to BCa. T1G3 patients do poorly, with 1 and 5 year disease progression rates of 11.4% and 19.8%, respectively, and 1 and 5 year disease specific death rates of 4.8% and 11.3%. Limitations include lack of repeat transurethral resection in high-risk patients and exclusion of patients with carcinoma in situ.

Conclusions: NMIBC patients treated with 1 to 3 years of maintenance BCG have a heterogeneous prognosis. Patients at high risk of recurrence and/or progression do poorly on currently recommended maintenance schedules. Alternative treatments are urgently required.

INTRODUCTION

European Association of Urology (EAU) recommendations for adjuvant treatment of non-muscle invasive bladder cancer (NMIBC) are based on risk groups: low, intermediate or high risk [1,2]. They are derived from European Organization for Research and Treatment of Cancer (EORTC) risk tables which provide probabilities of recurrence and progression after transurethral resection of the bladder (TURB) [3], but these patients didn't received maintenance bacilli Calmette-Guérin (BCG), which is now recommended for high risk patients. In 1062 patients treated with a maintenance schedule of six two-weekly BCG instillations for 5–6 months, the Club Urológico Español de Tratamiento Oncológico (CUETO) found that EORTC risk tables overestimated the overall risk of recurrence and the probability of progression in high risk patients [4]. Using these data, CUETO developed a model to stratify patients according to their risk of recurrence and progression [5,6] which also successfully stratified a patient's risk of recurrence after BCG plus interferon-alpha therapy [7].

The CUETO maintenance schedule is considerably shorter than the 1 to 3 years of maintenance BCG currently recommended by the EAU [1,2]. Prognostic factors for this longer maintenance schedule are unknown.

Our aim was to determine prognostic factors and the probabilities of recurrence, progression, disease specific survival (DSS) and overall survival (OS) in stage Ta-T1 NMIBC patients treated with 1 to 3 years of maintenance BCG and identify high-risk patients who may need early cystectomy. We also assess the performance of the CUETO models on EORTC data.

MATERIALS AND METHODS

Individual patient data were merged from two EORTC phase 3 trials (30911, 30962) in Ta-T1 NMIBC (without carcinoma in situ (CIS)) where patients were randomized to receive 1 or 3 years of maintenance Tice BCG [8,9] (See Appendix Supplement for study details). Treatment duration had no impact on determination of the prognostic factors. Its possible impact was diluted because 40-50% of patients randomized to 3 years of maintenance BCG in the two studies received ≤ 1 year, mainly due to inefficacy.

Patient and tumor characteristics previously investigated by the EORTC or CUETO were retrospectively analyzed: age, gender, prior recurrence rate, number of tumors, largest tumor diameter, tumor stage, and 1973 World Health Organization (WHO) grade.

The following endpoints were assessed:

Time to first recurrence (Disease Free Interval), defined as (1) early recurrence within the first 4.5 months after randomization (the time between randomization and first follow-up cystoscopy, normally at 3 months, which was delayed in some patients) or (2) time to late recurrence (the first recurrence in patients without an early recurrence who have follow-up after 4.5 months (Landmark analysis)). Patients still alive without recurrence were censored at the last follow-up. The time was censored at death and/or cystectomy in absence of recurrence (competing risk).

Time to progression was defined as the time from randomization to first increase to stage T2 or higher or development of metastases. Patients still alive without progression were

censored at the last follow-up. The time was censored upon death and/or cystectomy before progression (competing risks).

Duration of survival was defined as the time from randomization to death from any cause or last follow-up. For DSS deaths not due to bladder cancer (BCa) are competing risks. For both endpoints, patients still alive were censored at the last follow-up.

Median follow-up in all patients was estimated using the Kaplan-Meier technique and OS time but with status indicator reversed: Patients still alive were considered to have died at last follow-up, and patients who died were censored at date of death [10].

The dataset was split into two sets based on country: a training set from the largest participating countries for model development and a validation set (Appendix Table 1). Using previous publications as a guide [3,5,6], variables were coded based on training set univariate analyses.

In multivariate regression models for recurrence, variables were: age (continuous), gender, prior recurrence rate (primary versus ≤ 1 per year versus >1 per year), tumor size (< 3 cm versus ≥ 3 cm), number of tumors (< 4 versus ≥ 4 [6]), stage (Ta versus T1), and 1973 WHO grade (G1 versus G2-G3). For progression, time to death due to BCa and OS, the same variables and coding were used except for tumor size (continuous), number of tumors (< 8 versus ≥ 8) and grade (G1, G2 or G3).

For early recurrence, multivariable logistic regression models were fit using Bayesian Information Criterion (BIC) variable selection to allow covariates to leave the model [11].

For endpoints affected by competing risks, Fine and Gray regression models were fit using Bayesian Information Criterion for Competing Risks (BICcr) variable selection [12]. For overall survival, Cox regression models were fit based on BIC variable selection. Final models were based on the frequency of variables retained using BIC/BICcr selection procedures with bootstrap re-sampling.

Kaplan-Meier OS curves were estimated. Based on the multivariable model, a nomogram was constructed to predict 1 and 5 year survival. The nomogram provides a graphic representation linking an individual patient's multivariable prognostic factors to his or her survival probability. Goodness of fit was assessed with calibration plots. For other endpoints, time to event distributions were estimated using cumulative incidence curves.

Based on multivariable analyses in the training set, prognostic factors were identified and prognostic categories formed. Categories with similar prognoses were grouped together, with emphasis placed on identifying the best prognosis and the worst prognosis patients. These categories and survival regression coefficients were applied to the validation set.

The Area under the Curve (AUC) and Harrell's bias corrected concordance index (C index) were used to assess model accuracy (discrimination) in the training and validation datasets [13-14]. The C index is the probability that for two randomly chosen patients, the patient who had the event first has a higher probability of having the event according to the model. Consequently, $C = 0.50$ represents agreement by chance; $c = 1.0$ represents perfect discrimination.

For all endpoints, sensitivity analyses were done stratified by study. Sensitivity analyses also compared the results of Cox and the Fine and Gray models.

Statistical analyses were done in SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.0.1 (R Foundation, Vienna, Austria) with crsstep package v.2014-07.16, cmprsk package v. 2.2-7, and rms package v. 4.2-1 for constructing nomograms.

RESULTS

A total of 1812 Ta-T1 patients from EORTC studies 30962 (n=1272 patients) and 30911 (n=540) were included, 1180 (65%) of whom were allocated to 3 years of maintenance BCG and 632 (35%) to 1 year. They were divided into a training dataset with 1178 patients and a validation dataset with 634 patients.

Table 1. Patient characteristics

	Training (n=1178)	Validation (n=634)	Total (n=1812)
	n (%)	n (%)	n (%)
Age			
≤60	333 (28)	162 (26)	495 (27)
61-70	397 (34)	233 (37)	630 (35)
71-80	393 (33)	201 (32)	594 (33)
>80	55 (4.7)	38 (6.0)	93 (5.1)
Gender			
Female	199 (17)	101 (16)	300 (17)
Male	979 (83)	530 (84)	1509 (83)
Unknown	0 (0.0)	3 (0.5)	3 (0.2)
Prior recurrence rate			
Primary	635 (54)	358 (56)	993 (55)
Recurrent, ≤1/Year	220 (19)	121 (19)	341 (19)
Recurrent, >1/Year	297 (25)	137 (22)	434 (24)
Unknown	26 (2.2)	18 (2.8)	44 (2.4)
Largest tumor size			
≤1cm	517 (44)	306 (48)	823 (45)
>1cm - <3cm	354 (30)	196 (31)	550 (30)
≥3cm	247 (21)	112 (18)	359 (20)
Unknown	60 (5.1)	20 (3.2)	80 (4.4)
Number of tumors			
1	175 (15)	69 (11)	244 (13)
2-3	700 (59)	372 (59)	1072 (59)
4-7	253 (21)	138 (22)	391 (22)
≥8	50 (4.2)	55 (8.7)	105 (5.8)
T category			
Ta	807 (69)	345 (54)	1152 (64)
T1	370 (31)	289 (46)	659 (36)
Unknown	1 (0.1)	0 (0.0)	1 (0.1)
1973 WHO grade			
G1	389 (33)	191 (30)	580 (32)
G2	506 (43)	309 (49)	815 (45)
G3	280 (24)	132 (21)	412 (23)
Unknown	3 (0.3)	2 (0.3)	5 (0.3)

Median age was 67 years, 43% were recurrent, 24% had a prior recurrence rate > 1 per year, 87% had multiple tumors, 20% tumors \geq 3 cm in diameter, 36% were T1 and 23% had grade 3 tumors (Table 1). Patient characteristics in the training and validation datasets were similar, except for a higher percentage of T1 patients in the validation dataset (46% versus 31%).

After a median follow-up of 7.4 years, 6.7 years in patients still alive, 762 patients recurred, 173 progressed and 520 died, 83 due to BCa (Table 2).

Table 2. Number of events

	Training (n=1178)	Validation (n=634)	Total (n=1812)
	n (%)	n (%)	n (%)
Recurrence	509	253	762
Early recurrence	202 (17.1)	83 (13.1)	285 (15.7)
Late recurrence	307	170	477
Progression	116	57	173
Dead	318	202	520
Bladder cancer	59	24	83
Dead other cause	259	178	437

The 1 and 5 year recurrence rates were 25.9% (95% CI: 23.8%-27.9%) and 41.3% (95% CI: 39.0%-43.7%), respectively. (Appendix Figure 1).

Overall, 285 (15.7%) patients had an early recurrence (Table 2). Using the training data set, the final logistic model for early recurrence included prior recurrence, number of tumors, and grade. Table 3 shows the probabilities of early recurrence in the training and validation data sets in six prognostic groups. The best prognosis patients, G1 patients with less than 4 tumors and a prior recurrence rate \leq 1 per year, had an 8% probability of early recurrence in the validation set. The worst prognosis group, 4 or more G2 or G3 tumors and > 1 recurrence per year, had a 29% probability of early recurrence in the validation set. For these six groups, the Area under the curves (AUC) were 0.67 and 0.65 in the training and validation datasets, respectively.

Table 3. Probabilities of early recurrence and 95% confidence intervals in the training and validation datasets according to prognostic group

Six prognostic groups for early recurrence		Training dataset: AUC 0.67 % (95% CI)	Validation dataset: AUC 0.65 % (95% CI)
1	Grade 1 Prior recurrence $\leq 1/y$ <4 tumors	11/204 5 (0.03-0.09)	8/102 8 (0.04-0.15)
2	Grade 1 Prior recurrence $> 1/y$ <4 tumors	13/65 20 (0.12-0.31)	6/33 18 (0.08-0.35)
3	Grade 1 Prior recurrence $\leq 1/y$ ≥ 4 tumors	Grade 2 or 3 Prior recurrence $\leq 1/y$ <4 tumors 75/540 14 (0.11-0.17)	26/290 9 (0.06-0.13)
4	Grade 1 Prior recurrence $> 1/y$ ≥ 4 tumors	Grade 2 or 3 Prior recurrence $> 1/y$ <4 tumors 46/154 30 (0.23-0.37)	8/56 14 (0.07-0.26)
5	Grade 2 or 3 Prior recurrence $\leq 1/y$ ≥ 4 tumors	24/109 22 (0.15-0.31)	21/87 24 (0.16-0.34)
6	Grade 2 or 3 Prior recurrence $> 1/y$ ≥ 4 tumors	31/77 40 (0.30-0.51)	14/48 29 (0.18-0.43)
	Missing	2/29	0/18
	Total	202/1178	83/616

Late recurrence was observed in 477 patients (Table 2). A total of 375 patients were excluded from the analysis, 285 patients due to early recurrence and 90 patients due to absence of follow up after the landmark. Prognostic variables in the final model were prior recurrence rate and number of tumors. With these variables, 4 prognostic groups were created (Table 4). The best prognosis group (<4 tumors and ≤ 1 recurrence per year) has recurrence probabilities of 14.0% and 28.3% at 1 year and 5 years, respectively, in the validation set. The worst prognosis group, (≥ 4 tumors and > 1 recurrence per year) recurrence probabilities of 33.0% and 51.7%, respectively. The C-indexes in the training and validation data sets were 0,59 and 0,56, respectively. Cumulative incidence curves are provided in Figures 1a/b.

Table 4. Probabilities of late recurrence and 95% confidence intervals in the training and validation datasets according to prognostic group

	Training dataset (C-index 0.59)*		Validation dataset (C-index 0.56)*	
	1 year % (95% CI)	5 years % (95% CI)	1 year % (95% CI)	5 years % (95% CI)
Prior recurrence ≤1/y and < 4 tumors	11.0 (8.4-13.5)	25.9 (22.1-29.6)	14.0 (10.2-17.9)	28.3 (23.1-33.6)
Prior recurrence ≤1/y and ≥ 4 tumors	20.6 (13.9-27.3)	31.6 (23.7-39.5)	16.3 (8.5-24.1)	31.0 (20.8-41.3)
Prior recurrence >1/y and < 4 tumors	23.8 (16.5-31.2)	39.6 (30.9-48.2)	21.8 (11.3-32.3)	42.4 (29.3-55.5)
Prior recurrence >1/y and ≥ 4 tumors	31.2 (20.1-42.3)	55.4 (43.1-67.6)	33.0 (19.3-46.7)	51.7 (36.9-66.6)

*Maximum achievable C-index in both groups: 0.90 [13]

The multivariable model for disease progression identified two variables: grade and T category, with four prognostic groups (Table 5). The best prognostic group, TaG1 patients, had a progression probability of 1.9% at 1 year and 7.1% at 5 years in the validation data set. The group, T1G3 patients, had a progression probability of 11.4% at 1 year and 19.8% at 5 years (Table 5, Figures 2a and 2b). The C-indexes in the training and validation data sets were 0,72 and 0,64, respectively.

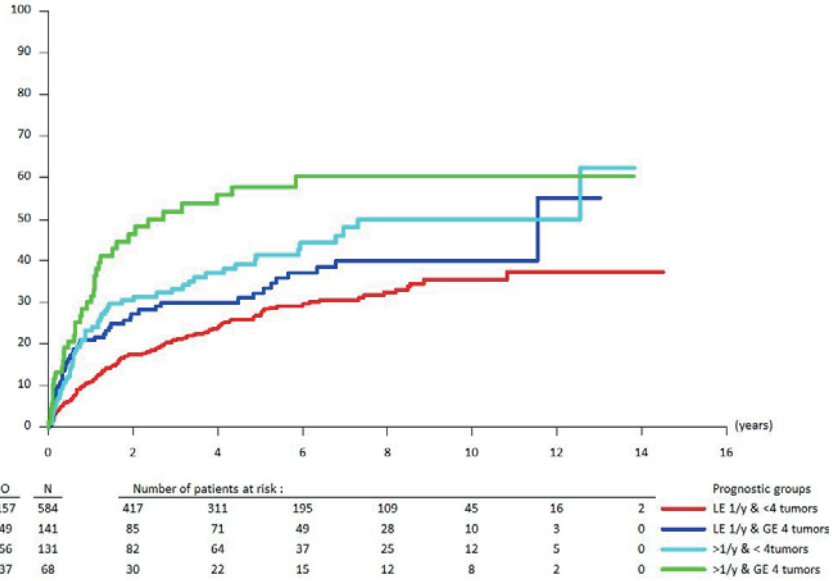
Table 5. Probabilities of progression and 95% confidence intervals in the training and validation datasets according to stage and grade

	Training data set (C-index 0.72)		Validation data set (C-index 0.64)	
	1 year % (95% CI)	5 years % (95% CI)	1 year % (95% CI)	5 years % (95% CI)
TaG1	0.28 (0-0.82)	2.4 (0.76-4.1)	1.9 (0-4.1)	7.1 (2.8-11.4)
TaG2 or T1G1	2.5 (0.97-4.0)	7.0 (4.4-9.6)	1.6 (0-3.4)	4.6 (1.5-7.7)
TaG3 or T1G2	3.5 (0.75-6.3)	15.2 (9.6-20.8)	1.8 (0-3.8)	5.9 (2.1-9.6)
T1G3	10.6 (6.5-14.7)	18.9 (13.6-24.4)	11.4 (5.3-17.5)	19.8 (12.0-27.6)

A total of 83 of 520 deaths were due to BCa. The same variables as for progression were of prognostic importance, grade and T category, and the same prognostic groups were formed (Table 6). TaG1, the best prognosis group, had a probability of death due to BCa of 1.5% at 5 years in the validation data set. The worst prognosis group, T1G3, has the highest probability of death due to BCa, 4.8% at 1 year and 11.3% at 5 years (Table 6). The C-indexes in the training and validation data sets were 0,72 and 0,71, respectively. The cumulative incidence curves are given in Figures 3a/b.

Figure 1. Time to late recurrence according to prognostic groups: (a) training set; (b) validation set.

(a)



(b)

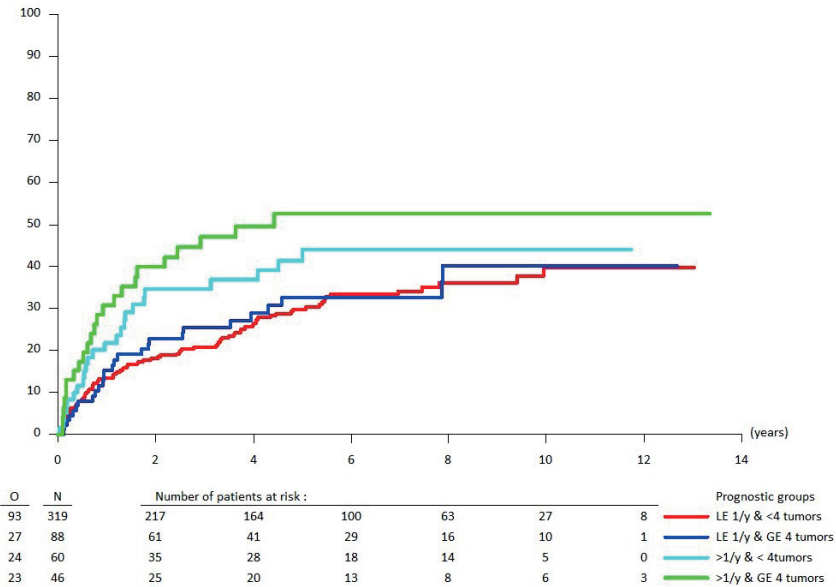


Table 6. Probabilities of death due to bladder cancer and 95% confidence intervals in the training and validation datasets according to stage and grade

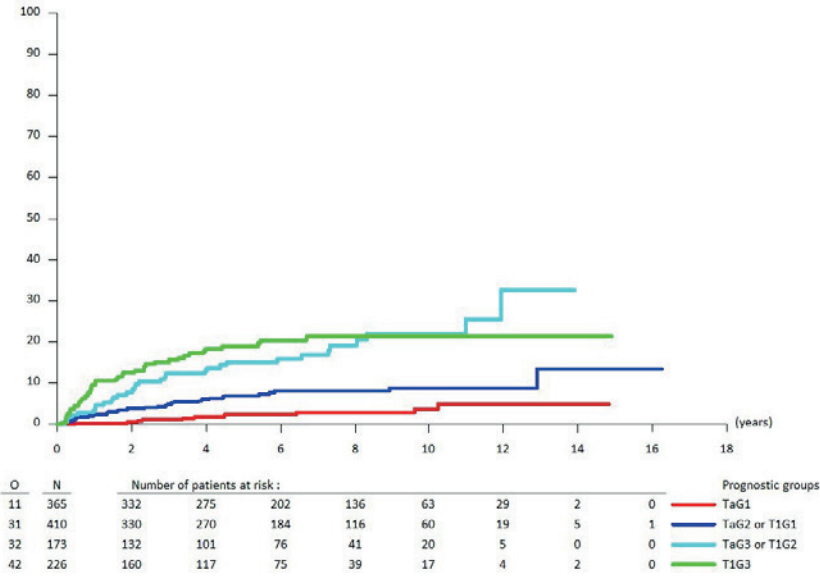
	Training data set (C-index 0.72)		Validation data set (C index 0.71)	
	1 year % (95% CI)	5 years % (95% CI)	1 year % (95% CI)	5 years % (95% CI)
TaG1	0 (no events)	0.87 (0-1.9)	0 (no events)	1.5 (0-3.6)
TaG2 or T1G1	0.75 (0-1.6)	3.6 (1.7-5.6)	0 (no events)	1.7 (0-3.6)
TaG3 or T1G2	0 (no events)	7.1 (3.1-11.2)	0 (no events)	1.4 (0-3.3)
T1G3	1.9 (0.05-3.7)	11.5 (6.9-16.0)	4.8 (0.70-8.9)	11.3 (5.0-17.6)

The final multivariable survival model included age and grade. The C indexes in the training and validation datasets were both 0.68. Model calibration of the selected model was checked with calibration plots (Appendix Figures 2a/b). Appendix Figures 3a, 3b and 4a present the Kaplan-Meier curves according to age and grade, respectively, in both datasets. Figure 4 provides a nomogram for survival based on age and grade. Points associated with the nomogram are given in Appendix Table 2. For example, a 65-year-old patient with a G3 tumor has 79 points (67 + 12), which results in survival probabilities of 97% at 1 year and 78% at 5 years. The sensitivity analyses gave the same conclusions for all end points.

CUETO recurrence and progression scores were calculated using the EORTC data [6]. Time to recurrence and time to progression cumulative incidence curves were estimated and are presented in Appendix Figures 5a and 5b. The CUETO model did not perform as well when applied to EORTC data. The C-indexes for recurrence and progression decreased from 0.64 to 0.48 and from 0.69 to 0.53, respectively. Applied to the EORTC data, the CUETO model underestimated the risk of recurrence in the good risk patients and overestimated the risk of progression at 5 years in the poorer risk patients.

Figure 2. Time to progression according to prognostic groups: (a) training set; (b) validation set.

(a)



(b)

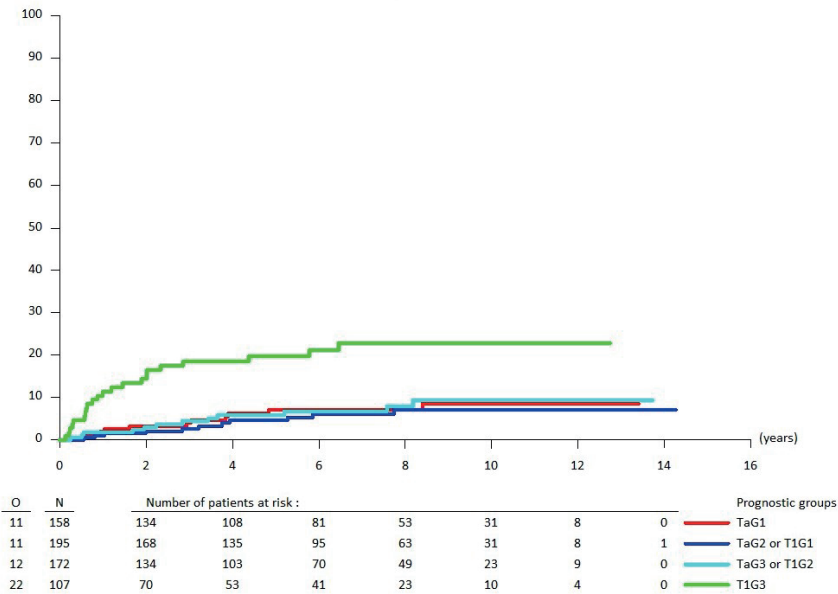
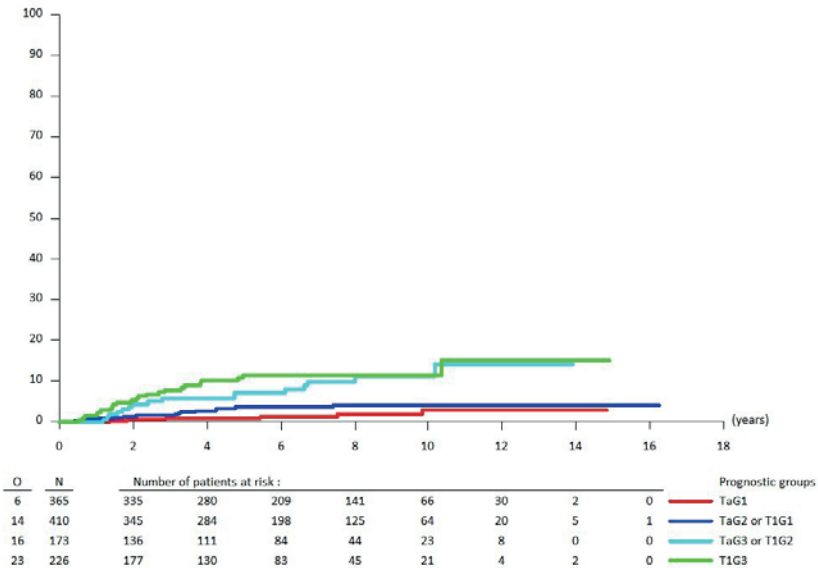


Figure 3. Disease-specific survival according to prognostic groups: (a) training set; (b) validation set.

(a)



(b)

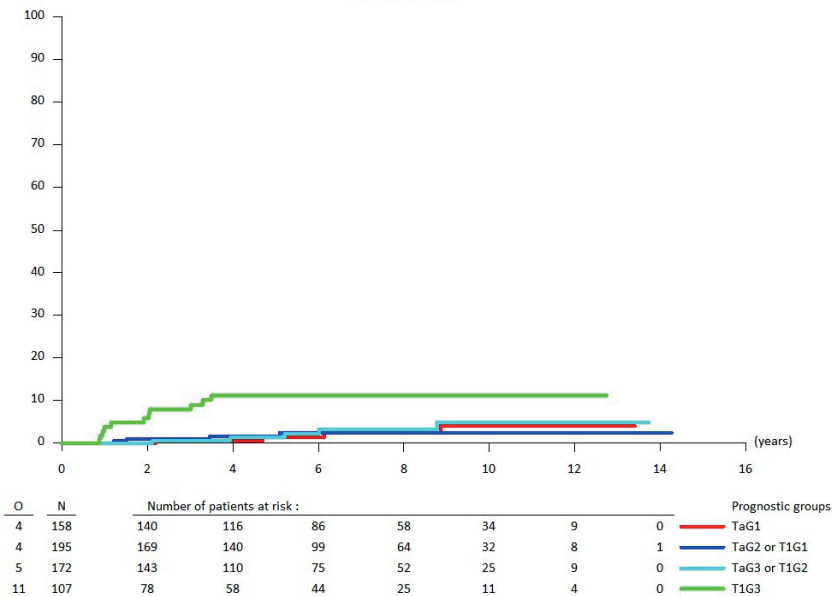
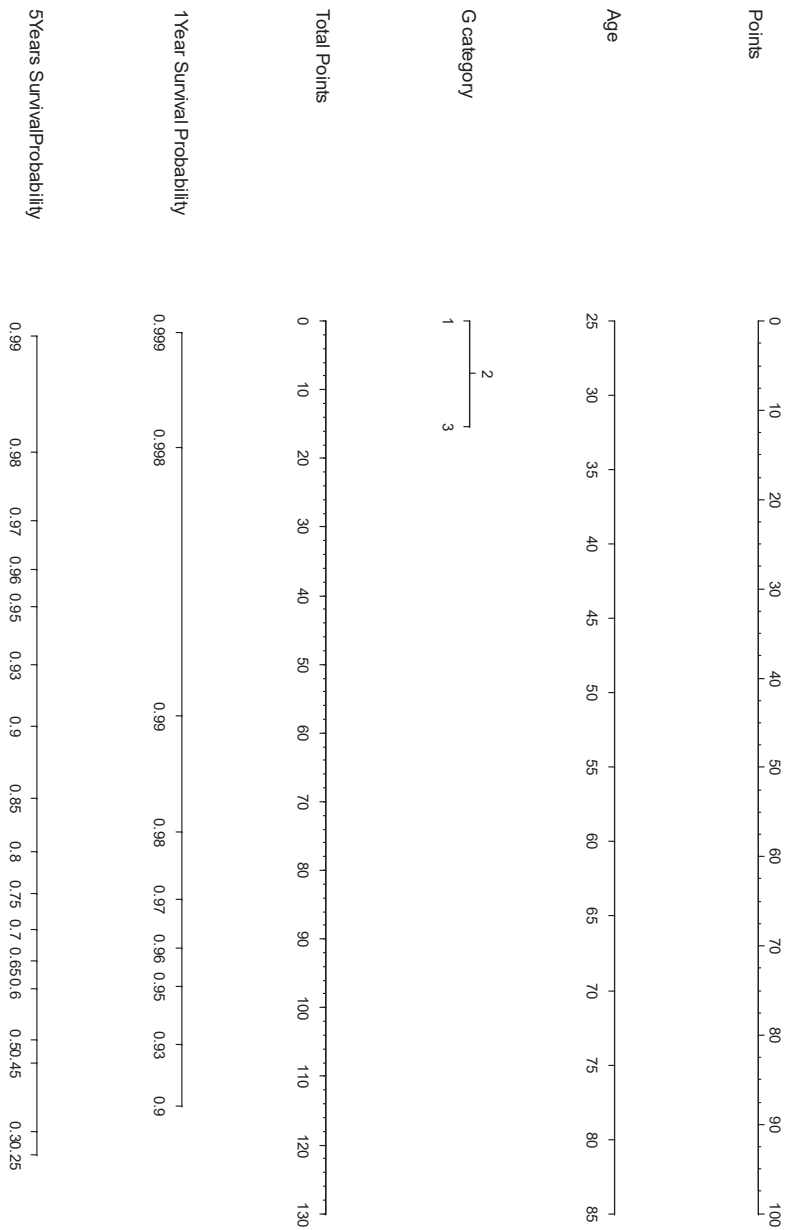


Figure 4. Nomogram for overall survival according to age and grade.



DISCUSSION

This paper presents the first prognostic factor analysis in NMIBC patients receiving the currently recommended 1 to 3 years of maintenance BCG and identified prognostic factors for recurrence, progression, DSS and OS.

The analysis made a distinction between early recurrence which may be influenced by unintended incomplete resection [15] and late recurrence in patients who are disease free at the first follow-up cystoscopy.

The most important prognostic factor for early recurrence were prior recurrence rate, number of tumors and grade. The prior recurrence rate and number of tumors were also the most important factors for time to recurrence in patients without an early recurrence. These results correspond with those from the EORTC [3] and CUETO [5-6]. However, CUETO also identified the prognostic importance of grade along with age and gender.

For progression, the most important factors were stage and grade which were also previously identified by the EORTC and CUETO. As expected, T1G3 patients had the worst prognosis with 1 and 5 yr progression rates of 11.4% and 19.8%, respectively.

CUETO models for recurrence and progression are “optimized” for their dataset and do not perform as well when applied to EORTC data. The longer duration of BCG in EORTC studies may have also had an impact on the results.

For the first time, prognostic factor analyses for both DSS and OS are provided. For DSS, the most important factors were the same as for progression: stage and grade. T1G3 patients had the worst prognosis with 1 and 5 yr disease specific death rates of 4.8% and 11.3%, respectively. Although grade remained statistically significant for OS, age was the dominant factor (Figure 4). The clinical utility of this nomogram in daily practice still needs to be proven. Patients previously identified as being at the highest risk of recurrence [3,5-6] still remain at the highest risk even when treated with 1 to 3 years of maintenance BCG. Patients with ≥ 4 tumors and a prior recurrence rate > 1 per year still have a probability of recurrence at 1 and 5 years of 33.0% and 51.7%, respectively, even if no tumor was detected at the first follow-up cystoscopy. With recurrences after more than 10 years, our study along with studies from CUETO, SWOG and FinnBladder have shown the need for long term follow-up in NMIBC patients [5,6,16,17].

Many patients do well on maintenance, with a 5 yr recurrence free rate of 58.7%. Although we can accurately identify the patients who do not progress or die due to their disease (approximately 95% of TaG1 patients do not progress, 98% do not die due to their disease), we cannot reliably identify the important subgroup of patients who do progress and die of their disease. Patients with T1G3 tumors, even without CIS, do relatively poorly, with 5 yr progression and disease specific death rates of 19.8% and 11.3%, respectively, but we need improved methods to identify the really high risk patients and develop effective treatments for them.

Because the number of tumors and the prior recurrence rate have also been shown to contribute to a worse prognosis, T1G3 patients with recurrent and/or multiple lesions should be considered for early cystectomy instead of BCG, especially if they have concomitant CIS, as

was concluded by Gontero et al [18]. However, we need better markers of immune response and molecular profiling to optimize patient selection and treatment strategy [19,20].

This dataset has a number of limitations. No patients with CIS were included. Both studies were carried out in an era when routine repeat transurethral resection was not performed in high risk patients. This could have contributed to under-staging that may have led to higher progression rates, especially in T1G3 patients. There was no central pathology review. No information was collected on the status of the upper urinary tract upon recurrence or progression, or on potential biomarkers. It was not possible to make a meaningful distinction between 1 year and 3 years of maintenance in the analysis. Nevertheless, this study provides the best available information about the prognosis of patients treated with the currently recommended 1 to 3 years of maintenance BCG.

CONCLUSIONS

NMIBC patients treated with 1 to 3 years of maintenance BCG have a heterogeneous prognosis for both the time to first recurrence (according to the prior recurrence rate and number of tumors) and the time to progression and death due to bladder cancer (based on tumor stage and grade).

Patients at high risk of recurrence and/or progression still do poorly on current maintenance schedules and alternative treatments are urgently required.

APPENDIX CHAPTER 4

Supplement: Study-specific details

1. Treatment

Treatment details are given in the respective publications [8,9]. No patients received an early post-operative instillation of chemotherapy. Treatment with BCG was to be started 15 days after TUR.

2. Follow Up

Three monthly cystoscopies and urinary cytology during at least the first two years was the recommended follow up schedule used in clinical practice at the time the studies were started. The same follow up schedule was used in both protocols:

Cystoscopy and urine cytology were repeated every 3 months during the first 3 years and every 6 months thereafter. All visible lesions had to be resected with recurrence established only by histological confirmation. If cytology was positive and no lesions were visible on cystoscopy, random biopsies had to be taken.

3. Treatment Completion

The main reason for stopping treatment was treatment inefficacy: disease recurrence or progression.

In trial 30911 [8], 149 patients (27%) completed all 3 years of treatment. 99 patients (18%) prematurely stopped treatment for toxicity.

In trial 30962 [9], 420 patients (66%) randomized to 1 year completed all 12 months of treatment and 246 patients (38%) randomized to 3 years completed all 36 months of treatment. 103 patients (8%) prematurely stopped treatment for toxicity.

4. Treatment Outcome

In trial 30962 [9], a statistically significant difference in time to recurrence between 1 and 3 years of treatment could not be detected, $p = 0.069$. There was no suggestion of a treatment difference for progression or survival. The possible impact of 3 years of maintenance on the determination of the prognostic factors is diluted by the events occurring already during the first year of treatment.

5. Further treatment after recurrence or progression

After stopping protocol treatment for any reason in trial 30911, 59 patients received further BCG, 57 patients received intravesical chemotherapy, and 25 patients had a cystectomy. In trial 30962, the data on further treatment are incomplete so further treatment was not analyzed, however 76 patients had a cystectomy.

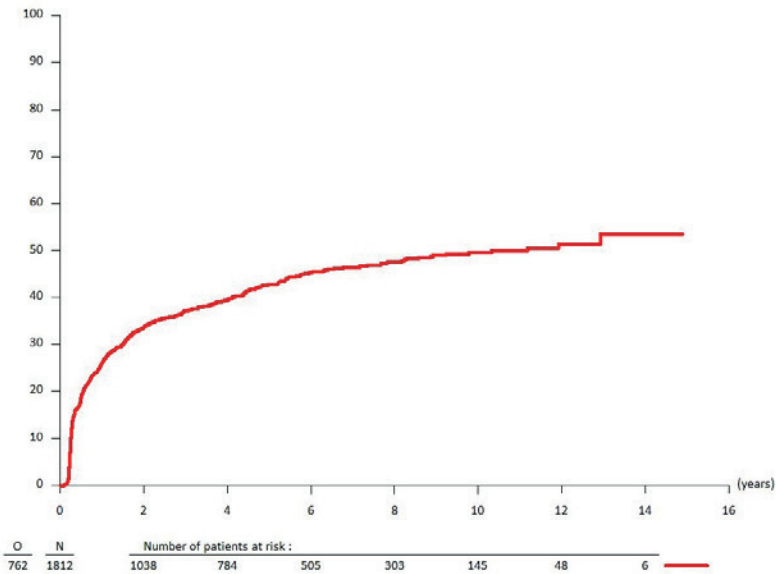
Appendix Table 1. Training and validation datasets

Training set (n= 1178)	Validation set (n=634)
Centers from:	Centers from:
Belgium	Austria
Italy	France
The Netherlands	Greece
	Israel
	Poland
	Portugal
	Romania
	Slovak Republic
	Spain
	Turkey
	UK

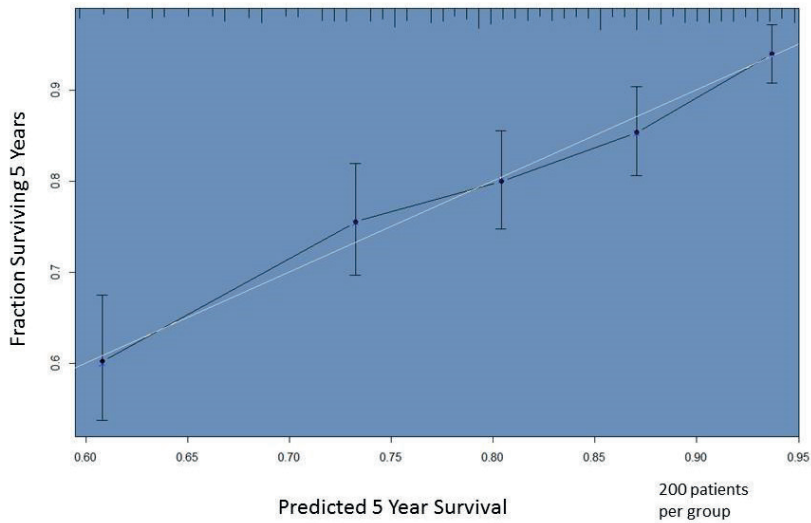
Appendix Table 2. Nomogram points for overall survival according to age and grade

Age	points
25	0
30	8
35	17
40	25
45	33
50	42
55	50
60	58
65	67
70	75
75	83
80	92
85	100
Grade	
G1	0
G2	6
G3	12

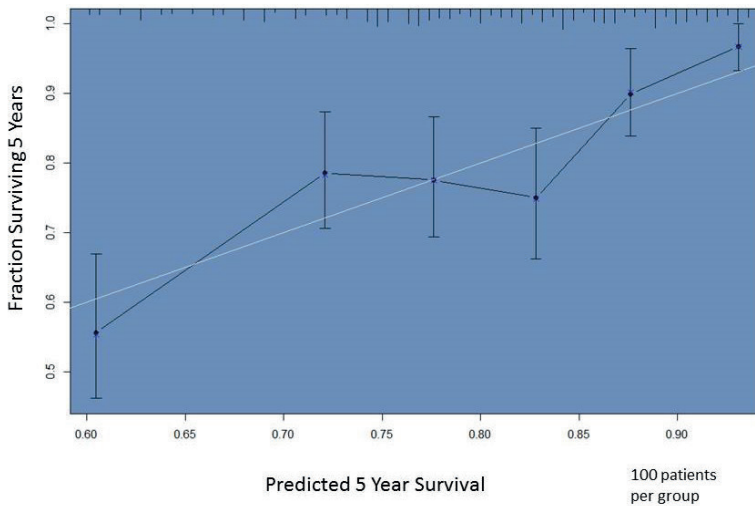
Appendix Figure 1. Time to first recurrence



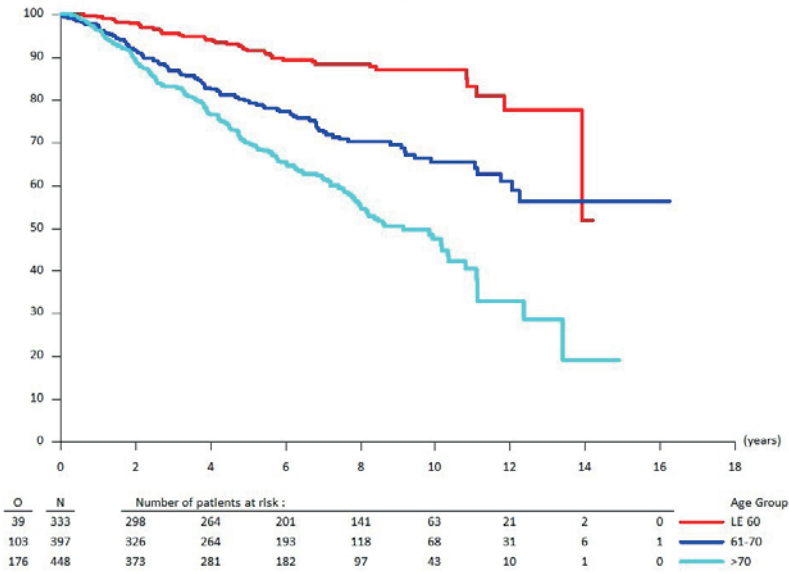
Appendix Figure 2a. Overall survival: calibration training set



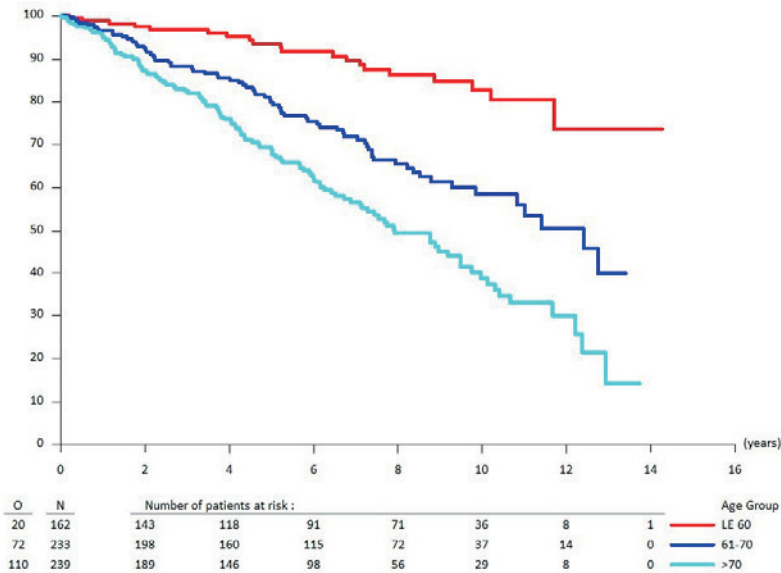
Appendix Figure 2b. Overall survival: calibration validation set



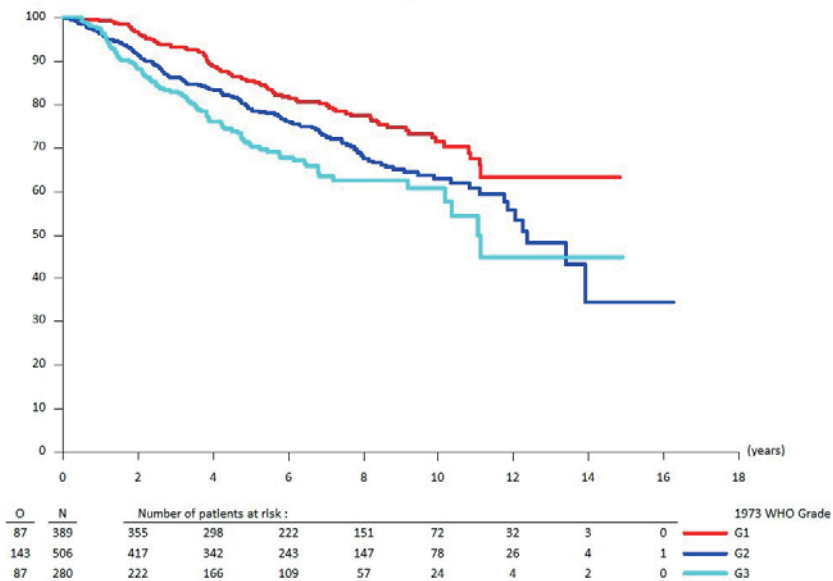
Appendix Figure 3a. Overall survival by age groups: training set



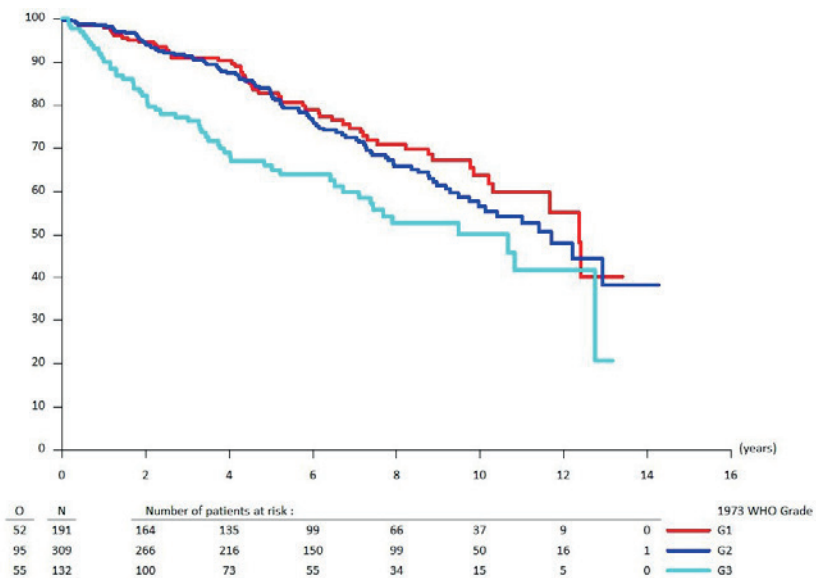
Appendix Figure 3b. Overall survival by age groups: validation set



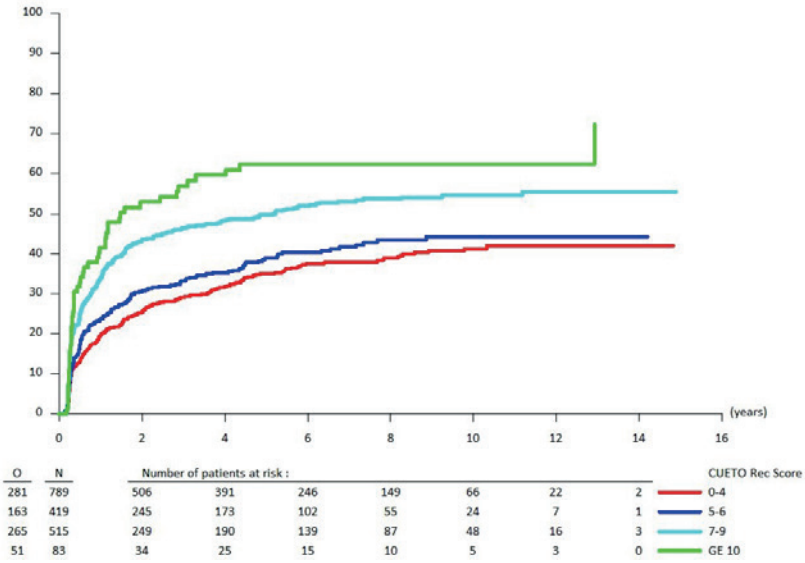
Appendix Figure 4a. Overall survival by grade: training set



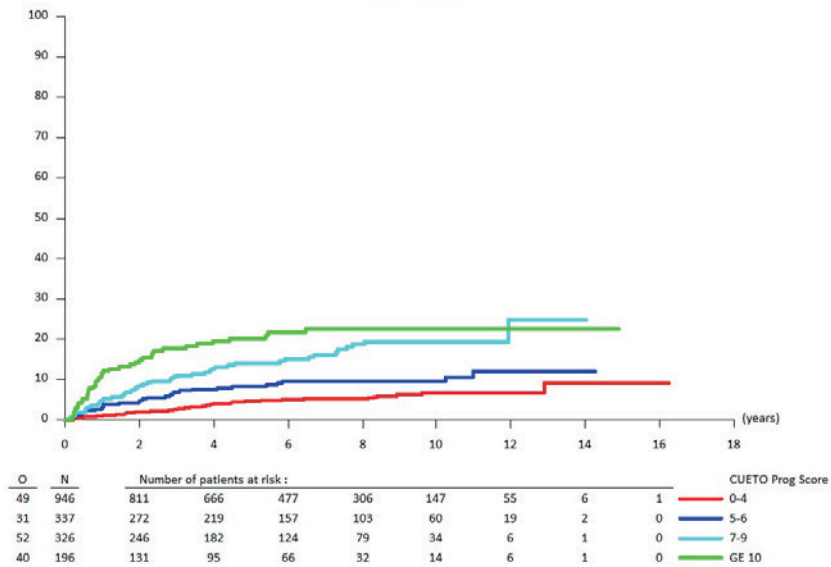
Appendix Figure 4b. Overall survival by grade: validation set



Appendix Figure 5a. Validation of CUETO model, time to first recurrence



Appendix Figure 5b. Validation of CUETO model, time to progression



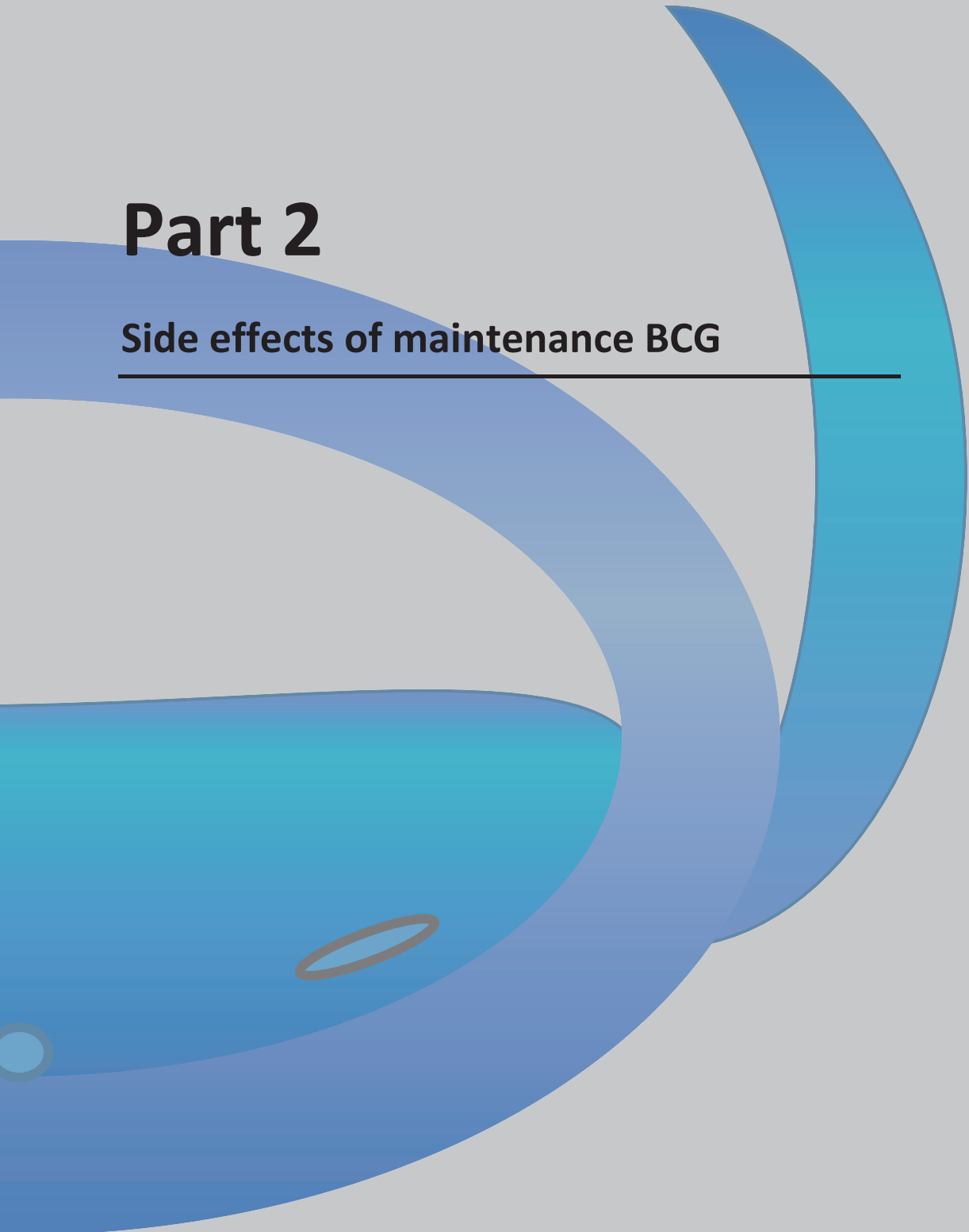
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Part 2

Side effects of maintenance BCG



Chapter 5

Side effects of bacillus Calmette-Guérin (BCG) in the treatment of intermediate and high risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC-GU Cancers Group randomized phase III study comparing 1/3 dose versus full dose and 1 year versus 3 years of maintenance BCG.

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ABSTRACT

Background: Although BCG has been proven to be highly effective in NMIBC it can cause severe local and systemic side effects (SE).

Objectives: The objective was to determine if reducing the dose or duration of BCG was associated with less SE. Efficacy comparisons of 1/3 dose (1/3D) versus full dose (FD) BCG given for 1 versus 3 years were previously published.

Design, Setting, Participants and Intervention: After TUR, patients with intermediate and high risk NMIBC without CIS were randomized to either 1/3D or FD BCG and 1 or 3 years of maintenance.

Outcome Measurements and Statistical Analysis: local and systemic SE were recorded at every instillation and were divided into 3 time periods: during induction, during the first year after induction, and during the 2nd and 3rd years of maintenance.

Results: In the 1316 patients who started BCG, 826 (62.8%) reported local SE, 403 (30.6%) systemic SE and 914 (69.5%) local or systemic SE. The percent of patients with at least one SE was similar in the 4 treatment arms ($p = 0.41$), both overall and in the different time periods. The most frequent local and systemic SE were chemical cystitis in 460 (35.0%) patients and general malaise in 204 patients (15.5%).

103 patients (7.8%) stopped treatment due to SE. No significant difference was seen between treatment groups ($p = 0.74$). In the 653 patients randomized to 3 years BCG, 35 (5.4%) stopped during the first year and 21 (3.2%) stopped in the 2nd or 3rd year.

Conclusions: No significant differences in SE were detected according to dose or duration of BCG treatment in the 4 arms. SE requiring treatment stop were seen more frequently in the 1st year, so not all patients are able to receive the one to three years of treatment recommended in current guidelines.

INTRODUCTION.

After transurethral resection (TUR), intravesical immunotherapy with Bacillus Calmette Guerin (BCG) is considered to be the most effective prophylactic treatment for patients with intermediate and high risk urothelial non muscle invasive bladder cancer (NMIBC) [1,2]. BCG induction instillations are classically given according to the empirical 6-weekly schedule that Morales introduced more than 35 years ago [3]. A number of randomized trials and meta-analyses published thereafter suggested that maintenance BCG instillations during 1 to 3 years is superior to both chemotherapy and induction BCG alone in reducing recurrences and even progression to muscle invasive disease [4-8]. As a result, current clinical practice guidelines recommend BCG with 1 to 3 years of maintenance as the intravesical therapy of choice for high-risk disease [1, 2].

Although BCG has been proven to be effective in Ta-T1 high grade tumors and CIS, it can produce moderate to severe local and systemic side effects. In Lamm's report on maintenance BCG, only 16% of patients were able to receive all instillations of the 3 yr treatment, mainly due to side effects [5]. More recently, in the report on EORTC trial 30911 comparing maintenance BCG ± isoniazid (INH) to epirubicin, 19% of patients in the BCG group had to stop treatment because of side effects, however 29% completed all 3 years of treatment [9].

The occurrence of side effects is one of the main reasons why urologists try to avoid the use of BCG, particularly in intermediate risk patients, for whom chemotherapeutic agents are often prescribed. Reduction in side effects might be achieved in several different ways: for example, with the administration of the antituberculosis drug INH [9,10,11] or the antibiotic ofloxacin [12] or by reducing the dose [13-15].

After EORTC trial 30911 showed that INH did not reduce side effects of BCG, EORTC study 30962 was designed with the primary objective to determine if 1/3 dose (1/3D) is not inferior to full dose (FD), if 1 year (1yr) maintenance is not inferior to 3 years (3yrs) maintenance and if 1/3D and 1yr maintenance are associated with less side effects.

As the efficacy results have already been reported [16], this article will focus on toxicity.

MATERIAL AND METHODS

Inclusion and exclusion criteria.

Patients with biopsy-proven, completely resected, solitary pT1G3 or multiple pTa-T1, grade 1–3 (1973 WHO classification) urothelial carcinoma of the bladder were included. Excluded were patients with solitary tumors except T1G3, more than 10 tumors, CIS, tumors stage T2 or higher, age > 85 yrs, WHO performance status 3 or 4, previous treatment with BCG and intravesical chemotherapy during the previous 3 months. An intravenous pyelography was performed to rule out upper tract tumors. Informed consent was obtained in accordance with the Declaration of Helsinki and/or existing national and local regulations.

Randomization and study interventions

Within 14 days after TUR, patients were randomized to one of four treatment groups:

1. 1/3 dose BCG with 1 yr maintenance (1/3D-1yr): BCG was given once a week for 6 wk, followed by 3 weekly instillations at months 3, 6, and 12. (A total of 4 cycles and 15 instillations.)
2. Full dose BCG with 1 yr maintenance (FD-1yr).
3. 1/3 dose BCG with 3 yr maintenance (1/3D-3yrs): BCG was given once a week for 6 wk, followed by 3 weekly instillations at months 3, 6, 12, 18, 24, 30 and 36. (A total of 8 cycles and 27 instillations.)
4. Full dose BCG with 3 yr maintenance (FD-3yrs).

For this study OncoTICE® (Organon-Teknika), containing 5×10^8 CFU, was used. 1/3 dose was prepared either by dissolving 1 vial with 150ml of saline and taking 50 ml or by dissolving with 50 ml, taking 17 ml, and diluting this to 50 ml.

Patients stopped protocol treatment at the second Ta/T1 recurrence after randomization and at progression to muscle-invasive disease, appearance of CIS, carcinoma in the upper urinary tract or prostatic urethra, or distant metastases. Further treatment was at the discretion of the local investigator.

Endpoints

The primary endpoint, the duration of the disease free interval (DFI), has been previously reported [16]. Secondary endpoints included the occurrence of side effects and their relationship to reduced dose or shorter duration of maintenance. The time of appearance of the side effects will also be addressed.

Side effects

At each instillation, patient complaints and symptoms were recorded as were urine cultures. Information about the presence or absence of local and systemic side effects and their impact on further treatment instillations was collected and reported during each cycle of protocol treatment according to a pre-defined format used in previous EORTC studies.

Local side effects included bacterial or chemical cystitis, frequency, hematuria, and other. Bacterial cystitis was defined as the occurrence of culture proven (not BCG related) cystitis. Irritative bladder symptoms with negative urine culture were classified as BCG induced (chemical) cystitis. Other local side effects included granulomatous prostatitis, epididymitis, ureteral obstruction and contracted bladder.

Systemic side effects included fever ($>39^{\circ}\text{C}$), influenza like symptoms including general malaise and chills, BCG induced lung infection, liver toxicity and BCG sepsis. Skin rash, arthralgia and arthritis were classified as possible allergic reactions.

The protocol provided recommendations for the treatment of BCG related complications (table 1). Based on the severity of the adverse effects, the treating physician decided whether instillations were to be postponed or even definitively stopped. In addition to an overall assessment of side effects, the treatment period was divided into 3 time intervals to evaluate when the side effects appeared:

1. The induction period (first 6 weekly instillations)
2. The first year of therapy after induction (next 9 instillations)
3. The second and third years of therapy (next 12 instillations, only in the 3 yr maintenance arms)

Table 1. Treatment recommendations for BCG-related complications as provided in the study-protocol

Complication	Recommended treatment
Fever < 38,5 °C, BCG cystitis, mild malaise	No treatment, hold BCG until symptoms resolve
Fever > 38,5 °C for 12-24 h	Isoniazid 300mg daily for 3 mo, may resume BCG when asymptomatic
Allergic reactions (arthralgia, myalgia, rash)	Isoniazid 300mg, further BCG is indicated only if benefit exceeds risk
Acute severe illness, local or systemic pneumonitis, hepatitis, prostatitis, ureteral obstruction, renal abscess, persisting high fever > 39 °C	Isoniazid 300mg, rifampin 600mg, ethambutol at 1200 mg daily for 6 months, no further BCG
BCG sepsis	Isoniazid 300mg, rifampin 600mg, ethambutol 1200mg cycloserine 500mg twice daily orally; confider prednisolone 40 mg immediately

In an analysis of side effects that led to the decision to definitely stop treatment, a distinction has been made between the first year of therapy and the 2nd and 3rd years of treatment (in the 3 yr maintenance arms) to judge whether continuing with a three-year maintenance schedule leads to a higher percentage of patients with severe toxicity.

The percent of patients experiencing side effects in the treatment groups was compared using the Pearson chi square statistic. P-values were not adjusted for multiple testing.

RESULTS

After the quality control exclusion of 450 patients from 6 institutions, 1355 patients were centrally randomized by 51 institutions from 13 European countries from March 1997 to April 2005. Seventy-five patients (5.5%) were ineligible. Delay between TUR and randomization (>21 days) and type of tumor were the most common reasons of ineligibility.

341 patients were randomized to 1/3 dose BCG for 1 year, 339 to full dose BCG for 1 year, 337 to 1/3 dose for 3 years and 338 to full dose BCG for 3 years (Figure 1).

Patient characteristics were generally well balanced between the arms. Patient and disease characteristics along with the efficacy results already have been published [16].

The amount of treatment actually received is listed in Table 2. 39 patients (2.9%) did not receive any treatment, 11 of whom were ineligible. 420 (61.8%) patients randomized to receive BCG maintenance for 1 year completed the treatment versus 246 (36.4%) patients randomized to receive BCG for 3 years. Globally, 650 of 1316 patients (49.4%) started but did not complete their treatment, the main reason being treatment inefficacy in 338 (25.7%) patients. Side effects as reason for stopping treatment occurred in 103 (7.8%) patients while in 221 (16.8%) patients, other reasons for stopping were reported (Figure 2).

Figure 1. CONSORT Diagram

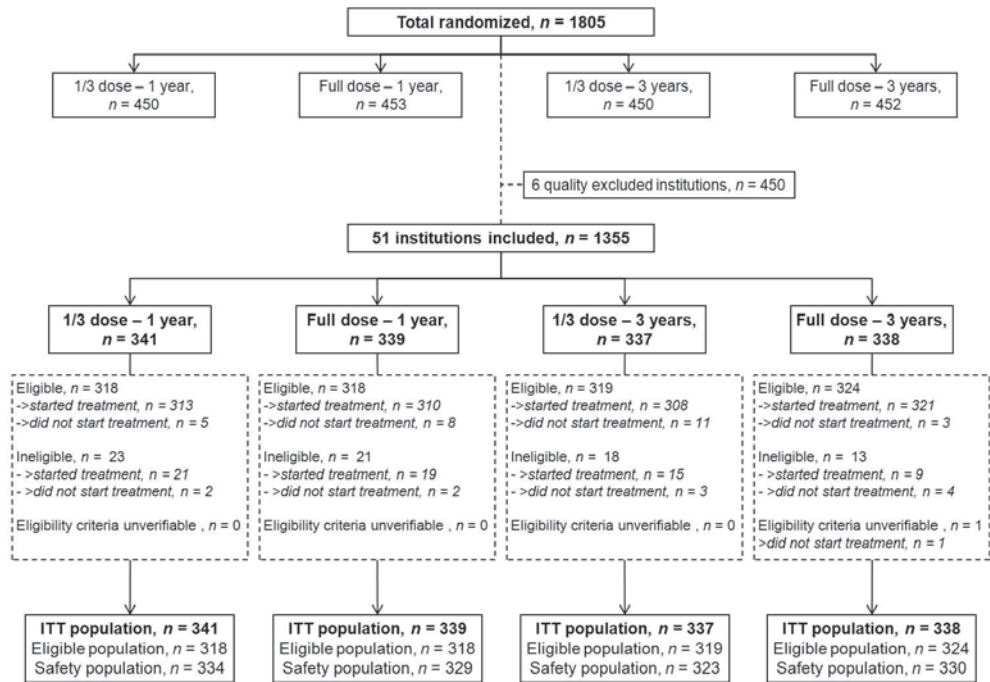


Table 2. Amount of treatment received

	BCG treatment arm			
	1/3 dose - 1yr (n=341)	Full dose - 1yr (n=339)	1/3 dose - 3yrs (n=337)	Full dose - 3yr (n=338)
	n (%)	n (%)	n (%)	n (%)
No treatment	7 (2.1)	10 (2.9)	14 (4.2)	8 (2.4)
Started treatment	334 (97.9)	329 (97.1)	323 (95.9)	330 (97.6)
Amount of treatment				
6 weeks	48 (14.1)	36 (10.6)	33 (9.8)	37 (10.9)
3 months	35 (10.3)	37 (10.9)	33 (9.8)	37 (10.9)
6 months	44 (12.9)	43 (12.7)	46 (13.6)	37 (10.9)
12 months	198 (58.1)	210 (61.9)	29 (8.6)	37 (10.9)
18 months	8 (2.3)	2 (0.6)	16 (4.7)	18 (5.3)
24 months	0	0	18 (5.3)	23 (6.8)
30 months	1 (0.3)	1 (0.3)	24 (7.1)	19 (5.6)
36 months	0	0	115 (34.1)	119 (35.2)
> 36 months	0	0	9 (2.7)	3 (0.9)
Completed Treatment	207 (60.7%)	213 (62.8%)	124 (36.8)	122 (36.1)

Figure 2. Reasons for stopping treatment

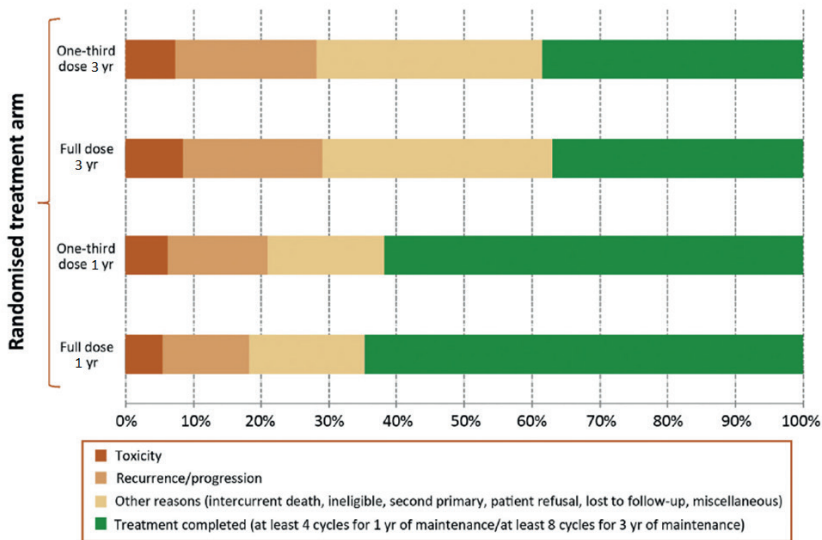


Table 3. Local and systemic side effects in all treatment arms (at any time).

	1 yr n (%)		3 yr n (%)		Total n (%)
	1/3 dose	Full dose	1/3 dose	Full dose	
<i>No of patients</i>	334	329	323	330	1316
Bacterial cystitis	71 (21,3)	69 (20,9)	89 (27,5)	77 (23,3)	306 (23,3)
Chemical cystitis	94 (28,2)	109 (33,1)	25 (39)	128 (38,7)	457 (34,7)
Other side effects	76 (22,8)	70 (21,2)	80 (24,5)	82 (24,8)	308 (23,4)
Frequency (>Once per hour)	63 (18,9)	76 (23,1)	87 (26,9)	84 (25,5)	310 (23,6)
Macroscopic Hematuria	73 (21,9)	78 (23,7)	77 (23,8)	70 (21,2)	298 (22,6)
Local side effects	195 (58.4)	205 (62.3)	217 (67.2)	209 (63.3)	826 (62.8)
Fever	17 (5.1)	29 (8.8)	27 (8.4)	33 (10.0)	106 (8.1)
Lung infection	2 (0.6)	1 (0.3)	0 (0.0)	2 (0.6)	5 (0.4)
Sepsis	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.6)	4 (0.3)
Skin rash	7 (2.1)	7 (2.1)	9 (2.8)	9 (2.7)	32 (2.4)
General malaise	42 (12.6)	51 (15.5)	49 (15.2)	62 (18.8)	204 (15.5)
Other systemic side effects	48 (14.4)	52 (15.8)	62 (19.2)	61 (18.5)	223 (16.9)
Systemic side effects	92 (27.5)	100 (30.4)	100 (31.0)	111 (33.6)	403 (30.6)
Local or systemic side effects	221 (66.2)	228 (69.3)	227 (70.3)	238 (72.1)	914 (69.5)

Treatment Comparisons:

- Local Side Effects: 4 treatment groups: $p = 0.14$; 1/3D versus FD (adjusted for duration of maintenance): $p = 0.98$; 1 yr versus 3 yr (adjusted for BCG dose): $p = 0.07$
- Systemic side effects: 4 treatment groups: $p = 0.40$; 1/3D versus FD (adjusted for duration of maintenance): $p = 0.28$; 1 yr versus 3 yr (adjusted for BCG dose): $p = 0.19$
- Local or systemic side effects: 4 treatment groups: $p = 0.41$; 1/3D versus FD (adjusted for duration of maintenance): $p = 0.33$; 1 yr versus 3 yr (adjusted for BCG dose): $p = 0.17$

In the 1316 patients who started BCG, 826 (62.8%) reported local SE, 403 (30.6%) systemic SE and 914 (69.5%) local or systemic SE. In Table 3, the various local and systemic side effects are listed by treatment. The percent of patients with local SE, systemic SE and local or systemic SE was similar in the 4 treatment groups ($p = 0.14$, 0.40 and 0.41, respectively). Likewise, no significant differences in the occurrence of side effects between the 1/3D and FD or 1 year and 3 years of maintenance groups were seen.

The most frequent side effects were local: chemical cystitis in 460 (35.0%) patients, bacterial cystitis in 307 patients (23.3%), frequency of more than once/hour in 310 patients (23.6%) and macroscopic hematuria in 298 patients (22.6%). Twenty-seven patients (2.1%) complained of urinary incontinence. The most frequent systemic SE were general malaise in 204 patients (15.5%) and fever in 106 patients (8.1%). Sepsis was observed in 4 patients (0.3%). When divided according to the time period of treatment (first 6 instillations, the first year of treatment after induction, and after 1 year of treatment (in treatment arms with 3 years of maintenance)), the distributions of side effects in the treatment groups were similar (Table 4).

Table 4. Local and systemic side effects in all treatment arms according to time of occurrence.

	During induction				During the first year of maintenance (after induction)				During years 2 and 3 of maintenance	
	n (%)				n (%)				n (%)	
	1 yr		3 yr		1 yr		3 yr		3 yr	
	1/3 D	FD	1/3 D	FD	1/3 D	FD	1/3 D	FD	1/3 D	FD
<i>No of patients</i>	334	329	323	330	286	293	290	293	182	182
Bacterial cystitis	49 (14.7)	55 (16.7)	48 (14.9)	42 (12.7)	33 (11.5)	31 (10.6)	43 (14.8)	43 (14.7)	23 (12.6)	20 (11.0)
Chemical cystitis	60 (18.0)	55 (16.7)	52 (16.1)	54 (16.4)	63 (22.0)	79 (27.0)	84 (29.0)	92 (31.4)	52 (28.6)	56 (30.8)
Other local side effects	34 (10.2)	38 (11.6)	40 (12.4)	31 (9.4)	53 (18.5)	50 (17.1)	43 (14.8)	43 (14.7)	30 (16.5)	31 (17.0)
Frequency (> once per hour)	25 (7.5)	38 (11.6)	27 (8.4)	20 (6.1)	45 (15.7)	54 (18.4)	44 (15.2)	56 (19.1)	40 (22.0)	35 (19.2)
Macroscopic hematuria	32 (9.6)	39 (11.9)	34 (10.5)	29 (8.8)	48 (16.8)	46 (15.7)	46 (15.9)	39 (13.3)	21 (11.5)	18 (9.9)
Local side effects	133 (39.8)	145 (44.1)	133 (41.2)	121 (36.7)	135 (47.2)	147 (50.2)	144 (49.7)	150 (51.2)	93 (51.1)	84 (46.2)
Fever	12 (3.6)	15 (4.6)	17 (5.3)	13 (3.9)	5 (1.7)	17 (5.8)	9 (3.1)	18 (6.1)	3 (1.6)	6 (3.3)
Lung infection	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Skin rash	4 (1.2)	4 (1.2)	2 (0.6)	5 (1.5)	3 (1.0)	4 (1.4)	5 (1.7)	4 (1.4)	4 (2.2)	1 (0.5)
General malaise	28 (8.4)	26 (7.9)	28 (8.7)	25 (7.6)	23 (8.0)	34 (11.6)	21 (7.2)	32 (10.9)	12 (6.6)	19 (10.4)
Other systemic side effects	24 (7.2)	35 (10.6)	22 (6.8)	28 (8.5)	31 (10.8)	27 (9.2)	36 (12.4)	34 (11.6)	21 (11.5)	20 (11.0)
Systemic side effects	57 (17.1)	63 (19.1)	52 (16.1)	53 (16.1)	51 (17.8)	62 (21.2)	60 (20.7)	66 (22.5)	33 (18.1)	33 (18.1)
Local or systemic side effects	160 (47.9)	172 (52.3)	149 (46.1)	143 (43.3)	153 (53.5)	165 (56.3)	160 (55.2)	175 (59.7)	100 (54.9)	93 (51.1)

In 207 (15.7%) patients, instillations were delayed or temporarily stopped due to side effects. Most treatment discontinuations due to side effects occurred within the first year: 103 patients (7.8%) stopped for toxicity, with 82 patients (6.2%) stopping during the first year. Among the 653 patients randomized to 3 yrs of BCG, 35 (5.4%) stopped during the first year of treatment due to side effects and 21 (3.2%) stopped during the second or third year (Tables 5 and 6).

Table 5. Definitive stop of instillations due to side effects in patients who started treatment (per treatment group)

Systemic or local side effects	BCG treatment arm				
	1/3 D - 1yr (n=334)	FD - 1yr (n=329)	1/3 D - 3yrs (n=323)	FD - 3yrs (n=330)	Total (n=1316)
	n (%)	n (%)	n (%)	n (%)	n (%)
Within 1st year	24 (7.2)	23 (7.0)	17 (5.3)	18 (5.5)	82 (6.2)
After the 1st year	0 (0.0)	0 (0.0)	9 (2.8)	12 (3.6)	21 (1.6)
Total	24 (7.2)	23 (7.0)	26 (8.1)	30 (9.1)	103 (7.8)

Comparison of the percent of patients stopping treatment due to side effects in the four treatment groups: $p = 0.74$.

Table 6. Definitive stop of instillations due to side effects in patients who started treatment (per treatment type)

Systemic or local side effects	BCG intervention			
	1/3 D (1yr + 3yrs) (n=657)	FD (1yr + 3yrs) (n=659)	1 yr (1/3D + FD) (n=663)	3 yrs (1/3D + FD) (n=653)
	n (%)	n (%)	n (%)	n (%)
Within the 1st year	41 (6.2)	41 (6.2)	47 (7.1)	35 (5.4)
After the 1st year	9 (1.4)	12 (1.8)	0 (0.0)	21 (3.2)
Total	50 (7,6)	53 (8,0)	47 (7,1)	56 (8,6)

DISCUSSION

Maintenance BCG has been advocated by many investigators as the therapy of choice for patients with Ta-T1 high grade urothelial carcinoma of the bladder and/or CIS. This is reflected in the various guidelines on NMIBC that include BCG as first line adjuvant therapy after TUR in high risk patients [1,2].

The most widely used maintenance schedule is based on the SWOG regimen starting with a 6 weekly induction series followed by three weekly instillations at 3 and 6 months and then every 6 months for 3 years [5]. Based on several meta-analyses, the EAU guidelines recommend at least 1 year of BCG maintenance therapy [1].

However, the side effects of BCG are well known and because of this, many urologists are reluctant to administer BCG to their patients, particularly when the disease is not high risk. It is therefore important to decrease BCG toxicity while maintaining its efficacy.

Many strategies have been advocated to reduce the side effects of BCG. In EORTC study 30911 with 3 years of maintenance BCG in intermediate and high risk patients, the prophylactic administration of INH did not decrease BCG's side effects. On the contrary,

transient liver function disturbances were encountered more frequently when INH was administered so the use of prophylactic INH is not recommended. [9, 15].

Another possible way to decrease BCG toxicity is by the administration of antibiotics at the time of BCG instillation. Colombel et al showed that 2 doses of Ofloxacin given shortly after BCG reduced side effects, however its effect on long term efficacy is unknown [12].

Recently, Johnson et al [17] showed that oxybutynin increased urinary frequency and burning on urination as compared to placebo and concluded that it should not be used in the routine prophylaxis against urinary symptoms during BCG therapy.

The most studied option is to decrease the dose. The EORTC-GU Group showed in a phase II marker lesion study that ¼ dose of BCG was active. [18].

The Club Urológico Español de Tratamiento Oncológico (CUETO) compared 1/3 dose of BCG to standard dose in intermediate and high risk patients. Reduced dose of BCG was as effective as full dose in intermediate risk patients but in high risk patients full dose provided the best results [13]. In a second study, in high risk patients (T1G3 and/or CIS), CUETO showed that 1/3 dose BCG was as effective as full dose against recurrence and progression but had significantly less toxicity. However, the number of patients who stopped BCG for toxicity did not differ significantly between the 2 arms [14]. A third report from CUETO found that 1/6 dose was significantly less effective than 1/3 dose for the treatment of intermediate-risk NMIBC suggesting that 1/3 dose is the minimum effective dose of BCG in these patients [15]. In these 3 reports, the maximum duration of maintenance BCG was only 5 months whereas in the current study the minimum treatment duration was one year. The purpose of EORTC study 30962 was to see if by reducing the dose of BCG to 1/3, the toxicity could be reduced while maintaining the same efficacy and to evaluate if 1 year maintenance was not inferior to 3 years with respect to efficacy.

The results of our study have shown that there were no significant differences in toxicity according to dose or duration of BCG treatment. 50 (7.6%) patients receiving 1/3 dose stopped treatment for toxicity versus 53 (8.0%) patients who received full dose BCG. 47 (7.1%) patients randomized to 1 yr maintenance stopped BCG for side effects versus 56 (8.6%) patients randomized to 3 yr. The additional 2 years of maintenance are not associated with an appreciable increase in toxicity.

These results on the discontinuation rate of BCG for toxicity are better than those observed in our previous study 30911 where 19.0% of patients had to stop BCG therapy for adverse events [19]. Likewise, for the most frequent side effects other than bacterial cystitis, the percent of patients reporting side effects tended to be lower in the current trial than in the previous study. The reason for this cannot be explained, but may be associated with a greater experience of urologists and nurses in administering BCG therapy nowadays. Our results confirm the observation from study 30911 that the majority of side effects occurred within the first year [19]. This suggests that systemic side effects depend mainly on the host and not on the number of instillations.

The awareness of possible adverse events when administering BCG together with the proper use of antituberculosis drugs can improve local or systemic side effects. In addition, a

meticulous discussion with patients receiving BCG on its efficacy and possible adverse events has been proven to improve patient compliance [20].

Limitations of this study include the lack of a placebo control arm, which is not ethical in this patient group, and the absence of standardized criteria to define intravesical BCG toxicity as a reason for postponing or stopping treatment. Although side effects were reported according to a pre-defined format used in previous studies, the clinical implications of the same adverse event could differ among investigators from unacceptable to normal drug activity. In the absence of validated international guidelines for the definition and treatment of side effects, the description of local and systemic side effects by expert urologists involved using pre-defined case report forms across many prospective, randomized EORTC studies could be considered as a surrogate standard.

CONCLUSIONS

No significant differences in toxicity were detected according to dose (1/3 versus FD) or duration (1 versus 3 years) of BCG treatment in the 4 arms. Neither reducing the dose nor shortening the duration of maintenance decreased the percent of patients who stopped treatment due to side effects. Side effects requiring treatment stop were seen more frequently in the first year of therapy, preventing some patients from receiving the one to three years of treatment recommended in current guidelines.

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Chapter 6

Increasing age is not associated with toxicity leading to discontinuation of treatment in urothelial non muscle invasive bladder cancer patients randomized to receive 3 years of maintenance bacillus Calmette-Guérin: Results from EORTC GU Group study 30911.

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ABSTRACT

Objectives: To determine the relationship of age to side effects leading to discontinuation of treatment in stage Ta-T1 NMIBC patients treated with maintenance bacillus-Calmette-Guérin (BCG).

Patients and Methods: We evaluated toxicity for 487 eligible intermediate or high risk Ta-T1 (without CIS) non-muscle-invasive bladder cancer (NMIBC) patients randomized to receive 3 years of maintenance BCG (247 BCG alone and 240 BCG+INH) in EORTC trial 30911. The percent of patients who stopped for toxicity and the number of treatment cycles that they received were compared in 4 age groups, ≤ 60 , 61 - 70, 71 – 75 and > 75 years of age, using the Mantel-Haenszel chi square test for trend.

Results: The percent of patients stopping BCG for toxicity was 17.9% in patients ≤ 60 , 21.9% in patients 61 – 70, 22.9% in patients 71 – 75, and 16.4% in patients > 75 years of age ($p = 0.90$). For both systemic and local side effects, there was likewise no significant difference.

Conclusions: In intermediate and high risk Ta T1 urothelial bladder cancer patients treated with BCG, no differences in toxicity as a reason for stopping treatment were observed based on age.

INTRODUCTION

In the 2015 European Association of Urology (EAU) guidelines, adjuvant treatment of intermediate- and high-risk urothelial non muscle invasive bladder carcinoma (NMIBC) patients with bacillus Calmette-Guérin (BCG) is standard of care. The recommended schedule consists of an induction course of six weekly instillations followed by a maintenance schedule of one year in intermediate-risk patients, in whom intravesical chemotherapy is also an option, and one to three years of BCG in high-risk patients [1].

Although there isn't a significant effect of age on time to recurrence in patients receiving BCG, patients > 70 years of age do have a significantly shorter time to progression, overall survival and disease specific survival compared to patients \leq 70 years of age. Nevertheless, BCG is still more effective than epirubicin even in elderly patients [2].

Side effects of BCG as a reason for stopping treatment occurred in 19% of the patients in EORTC study 30911 [3]. A relationship between side effects and efficacy was not seen [4].

On the basis of a small retrospective cohort of 58 patients aged 51 to 92 years, Heiner et al. suggested that side effects were more common in the elderly [5]. They concluded that one should be careful with BCG maintenance treatment in patients over 70 years of age and even suggested to avoid it in patients over the age of 80. Other reports on this subject are lacking. The median age of bladder cancer patients is 69 years for men and 71 years for women [6]. It is expected that with the rising of age of the population, the prevalence of bladder cancer will rise too.

In order to balance the advice to elderly patients for adjuvant BCG treatment, it thus becomes increasingly important to be aware of the possible relationship between age and the chances of stopping BCG maintenance due to side effects.

The objective of this paper is to determine if there is a correlation between age and stopping treatment due to side effects in NMIBC patients treated with BCG.

MATERIAL AND METHODS

EORTC GU Group study 30911 is one of the largest prospective randomized studies assessing the efficacy and side effects of 3 years of maintenance BCG treatment [3]. Patients with single or multiple, primary or recurrent, completely resectable stages Ta and T1, grades 1 to 3, histologically proven urothelial NMIBC were included. Exclusion criteria were a primary solitary tumor, muscle invasive tumor or carcinoma in situ, age older than 85 years, WHO performance status 3 or 4, and previous treatment with doxorubicin, epirubicin or BCG intravesical treatment during the previous 3 months. Tumors were classified according to the 1992 TNM classification of the International Union against Cancer [7].

Within 24 hours after transurethral resection (TUR), before receiving the definitive histology report, patients were randomized to one of three adjuvant treatment arms: epirubicin 50 mg in 50 ml of saline weekly for six consecutive weeks starting within 24 hours after transurethral resection or BCG (TICE®) weekly +/- isoniazid (INH) for six consecutive weeks starting seven to 15 days after transurethral resection. In all groups, the initial six instillations were followed by three weekly instillations at months 3, 6, 12, 18, 24, 30 and 36. Cytology and cystoscopy were

performed every three months during the first three years and every six months thereafter. In case of a suspected recurrence, pathological confirmation by a TUR was mandatory. The primary endpoint was the time to first bladder recurrence with secondary endpoints time to progression (muscle invasion or distant metastases), overall duration of survival, and time to death due to bladder cancer. Efficacy results and the effect of age and toxicity on efficacy have been previously published [2,3,4].

At each instillation, patient complaints and symptoms were recorded as were urine cultures. Information about the presence or absence of local and systemic side effects and their impact on further treatment instillations were collected and reported during each cycle of protocol treatment according to a pre-defined format used in previous EORTC studies.

Local side effects included bacterial or chemical cystitis, frequency, hematuria, and other. Bacterial cystitis was defined as the occurrence of culture proven (not BCG related) cystitis. Irritative bladder symptoms with negative urine culture were classified as BCG induced (chemical) cystitis. Other local side effects included granulomatous prostatitis, epididymitis, ureteral obstruction and contracted bladder.

Systemic side effects included fever (>39°C), influenza-like symptoms including general malaise and chills, BCG induced lung infection, liver toxicity and BCG sepsis. Skin rash, arthralgia and arthritis were classified as possible allergic reactions.

The protocol described treatment recommendations for moderate to severe local and systemic BCG-related complications (Table 1). Herein, reasons for stopping or delaying treatment are embedded. In the study case report forms, no information was collected about treatments given for side effects. The protocol didn't give recommendations for the use of dose reduction or prophylactic distribution of antibiotics in order to prevent side effects.

Table 1. Treatment recommendations for BCG-related complications as in study protocol.

Complication	Recommended treatment
Fever < 38,5 °C, BCG cystitis, mild malaise	No treatment, hold BCG until symptoms resolve
Fever > 38,5 °C for 12-24 h	Isoniazid 300mg daily for 3 mo, may resume BCG when asymptomatic
Allergic reactions (arthralgia, myalgia, rash)	Isoniazid 300mg, further BCG is indicated only if benefit exceeds risk
Acute severe illness, local or systemic pneumonitis, hepatitis, prostatitis, ureteral obstruction, renal abscess, persisting high fever > 39 °C	Isoniazid 300mg, rifampin 600mg, ethambutol at 1200 mg daily for 6 months, no further BCG
BCG sepsis	Isoniazid 300mg, rifampin 600mg, ethambutol 1200mg cycloserine 500mg twice daily orally; confider prednisolone 40 mg immediately

In earlier reports on BCG and the influence of age, the older group was defined as > 70 years of age [2,5,8]. As patients older than 70 years are increasingly seen in daily practice, we created 4 age groups, ≤ 60 , 61 - 70, 71 - 75 and > 75 years, in order to study the effects of age taking into account all age groups.

To determine the effect of age in relation to stopping treatment due to toxicity, the percent of patients stopping BCG for this reason, both overall and also separately due to local or systemic side effects, was compared in these 4 age groups using the Mantel-Haenszel chi square test for trend on 1 degree of freedom. The number of cycles of treatment in patients who stopped treatment for toxicity was compared in the four age groups using the Mantel-Haenszel chi square test for trend on rank scores with 1 degree of freedom.

Since we are especially interested in the two groups ≤ 70 years and > 70 years based on previous publications, we also compared the percent of patients stopping treatment for toxicity in these two groups using a continuity adjusted chi square test on 1 degree of freedom. The number of cycles of treatment in patients who stopped treatment for toxicity was compared in these two age groups using the Mantel-Haenszel chi square test on rank scores with 1 degree of freedom.

RESULTS

Between January 1992 and February 1997, 957 patients with intermediate or high risk stage Ta T1 urothelial bladder cancer were randomized by 44 institutions to receive adjuvant intravesical instillations after TUR: 318 to epirubicin and 639 to BCG (320 to BCG alone and 319 to BCG plus INH). 512 of the 639 patients were eligible with information on age, of whom 25 patients without information on BCG toxicity were excluded, ranging from four patients (2.9%) in the ≤ 60 years old group to five patients (7.6%) in the > 75 years old group. 487 patients started treatment and had follow up information on BCG toxicity (247 BCG alone and 240 BCG+INH) and were included in this analysis. Table 2 provides the distribution of patient characteristics by age group: 134 patients (27.5%) were ≤ 60 years of age, 187 (38.4%) were 61 – 70, 105 (21.6%) were 71 – 75 and 61 (12.5%) were > 75 years. Only 17 patients (3.5%) were > 80 years of age and were thus included in this last subgroup of patients > 75 years.

Table 2. Patient Characteristics

	≤ 60 years n (%)	61 - 70 years n (%)	71 – 75 years n (%)	>75 years n (%)	Total n (%)
Sex					
Male	111 (82.8)	147 (78.6)	78 (74.3)	43 (70.5)	379 (77.8)
Female	23 (17.2)	40 (21.4)	27 (25.7)	18 (29.5)	108 (22.2)
Tumor Status					
Primary	56 (41.8)	86 (46.0)	38 (36.2)	27 (44.3)	207 (42.5)
Recurrent	78 (58.2)	101 (54.0)	67 (63.8)	34 (55.7)	280 (57.5)
Tumor Size					
< 1 cm	67 (50.0)	88 (47.1)	59 (56.2)	28 (45.9)	242 (49.7)
1 – 3 cm	42 (31.3)	80 (42.8)	35 (33.3)	26 (42.6)	183 (37.6)
> 3 cm	19 (14.2)	13 (6.9)	7 (6.7)	6 (9.8)	45 (9.2)
Unknown	6 (4.5)	6 (3.2)	4 (3.8)	1 (1.6)	17 (3.5)
Number of Tumors					
Single	27 (20.1)	36 (19.3)	16 (15.2)	4 (6.6)	83 (17.0)
Multiple	105 (78.4)	150 (80.2)	87 (82.9)	56 (91.8)	398 (81.7)
Unknown	2 (1.5)	1 (0.5)	2 (1.9)	1 (1.6)	6 (1.2)
T Category					
Ta	92 (68.7)	113 (60.4)	68 (64.8)	28 (45.9)	301 (61.8)
T1	42 (31.3)	74 (39.6)	37 (35.2)	33 (54.1)	186 (38.2)
1973 WHO Grade					
G1	70 (52.2)	60 (32.1)	38 (36.2)	15 (24.6)	183 (37.6)
G2	50 (37.3)	101 (54.0)	50 (47.6)	38 (62.3)	239 (49.1)
G3	13 (9.7)	26 (13.9)	16 (15.2)	8 (13.1)	63 (12.9)
Unknown	1 (0.7)	0	1 (1.0)	0	2 (0.4)
Total	134	187	105	61	487

A total of 159 patients (32.6%) completed the maintenance schedule, 99 (20.3%) stopped treatment due to BCG toxicity and 80 (16.4%) stopped due to inefficacy. 149 patients (30.6%) stopped treatment due to other reasons (Table 3).

The percent of patients stopping BCG for toxicity was similar in the four age groups: 24 patients (17.9%) ≤ 60 years of age, 41 patients (21.9%) 61 - 70 years, 24 patients (22.9%) 71 - 75 years, and 10 (16.4%) patients > 75 years, chi square = 0.016, p = 0.90 (Table 3). There was likewise no difference in the percent of patients ≤ 70 years (20.2%) and > 70 years (20.5%) who stopped for toxicity, chi square = 0.00, p = 1.0.

Table 3. Reason for stopping treatment

	≤ 60 years n (%)	61 – 70 years n (%)	71 – 75 years n (%)	>75 years n (%)	Total n (%)
Not stopped due to toxicity	110 (82.1)	146 (78.1)	81 (77.1)	51 (83.6)	388 (79.7)
Stopped due to toxicity	24 (17.9)	41 (21.9)	24 (22.9)	10 (16.4)	99 (20.3)
Local only	14 (10.4)	24 (12.8)	10 (9.5)	5 (8.0)	53 (10.9)
Systemic only	5 (3.7)	9 (4.8)	10 (9.5)	2 (3.3)	26 (5.3)
Local and systemic	5 (3.7)	8 (4.3)	3 (2.9)	3 (4.9)	19 (3.9)
Type unknown	0	0	1 (0.1)	0	1
Stopped due to inefficacy or other reasons	61 (45.5)	84 (44.9)	48 (45.7)	36 (59.0)	229 (47.0)
Completed treatment	49 (36.6)	62 (33.2)	33 (31.4)	15 (24.6)	159 (32.6)
Total	134	187	105	61	487

45 patients stopped treatment due to systemic toxicity, 10 (7.5%) aged ≤ 60 years, 17 (9.1%) aged 61 - 70 years, 13 (12.4%) aged 71 - 75 years, and 5 (8.2%) > 75 years, chi square = 0.497, $p = 0.48$ (Table 4). Comparing patients ≤ 70 years and patients > 70 years, there was likewise no difference with chi square = 0.509, $p = 0.48$.

Table 4. Treatment stopped due to systemic BCG toxicity

Reason to stop for systemic side effects	< 60 years n (%)	61 - 70 years n (%)	71 - 75 years n (%)	>75 years n (%)	Total n (%)
Not stopped	124 (92.5)	170 (90.9)	92 (87.6)	56 (91.8)	442 (90.8)
Fever	4 (3.0)	8 (4.3)	9 (8.6)	2 (3.3)	23 (4.7)
Lung infection	0	1 (0.5)	0	0	1 (0.2)
Skin rash	1 (0.7)	0	0	0	1 (0.2)
General malaise	3 (2.2)	6 (3.2)	3 (2.9)	3 (4.9)	15 (3.1)
Other systemic side effects	2 (1.5)	2 (1.1)	1 (1.0)	0	5 (1.0)
Total	134	187	105	61	487

72 patients stopped treatment due to local toxicity, 19 (14.8%) aged < 60 years, 32 (17.1%) aged 61 - 70 years, 13 (12.4%) aged 71 – 75 years, and 8 (13.1%) aged > 75 years, chi square = 0.239, $p = 0.62$ (Table 5). Comparing patients ≤ 70 years and patients > 70 years, there was once again no difference with chi square = 0.671, $p = 0.41$.

Table 5. Treatment stopped due to local BCG toxicity

Reason to stop for local side effects	≤ 60 years n (%)	61 - 70 years n (%)	71 - 75 years n (%)	>75 years n (%)	Total n (%)
Not stopped	115 (85.2)	155 (82.9)	92 (87.6)	53 (86.9)	415 (85.2)
Bacterial cystitis	2 (1.5)	3 (1.6)	1 (1.0)	1 (1.6)	7 (1.4)
Chemical cystitis	8 (6.0)	19 (10.2)	6 (5.7)	5 (8.2)	38 (7.8)
Other local side effects	2 (1.5)	3 (1.6)	1 (1.0)	0	6 (1.2)
Type of local toxicity unknown	7 (5.2)	7 (3.7)	5 (4.7)	2 (3.3)	21 (4.3)
Total	134	187	105	61	487

The duration of treatment in patients who stopped for toxicity is given in Table 6. Although there is a suggestion that older patients may have stopped treatment earlier, neither the difference between the four age groups (chi square = 3.196 and p = 0.07) nor the difference between the two age groups (≤ 70 versus > 70 years) is statistically significant (chi square = 3.240 and p = 0.07).

Table 6. Duration of treatment in patients stopping for toxicity

Treatment Duration	≤ 60 years n (%)	61 - 70 years n (%)	71 - 75 years n (%)	>75 years n (%)	Total n (%)
Induction only	5 (20.8)	11 (26.8)	9 (37.5)	5 (50.0)	30 (30.3)
3 – 12 months	11 (45.8)	17 (41.5)	11 (45.8)	3 (30.0)	42 (42.4)
18 – 24 months	5 (20.8)	6 (14.6)	0	1 (10.0)	12 (12.1)
> 24 months	3 (12.5)	7 (17.1)	4 (16.7)	1 (10.0)	15 (15.2)
Total	24	41	24	10	99

The percent of patients who stopped treatment for toxicity was higher in the BCG + INH group (58 of 240 patients, 24.2%) as compared to the BCG alone group (41 out of 247 patients, 16.6%), however the overall conclusions with respect to age did not change when the two treatment groups were analyzed separately.

DISCUSSION

This is the largest study on BCG maintenance therapy that focuses on the relationship of age and toxicity as a reason for discontinuation of this treatment. Elderly patients have a worse outcome on BCG as far as efficacy is concerned [2], but we have now found that the risk of stopping treatment for toxicity in elderly patients is similar to that in younger patients. In an earlier report on data from the same study, no relationship between toxicity and efficacy, regardless of age, was found [4].

BCG induces a local immunological reaction inside the bladder wall. This results in secretion of various cytokines in urine. The level of cytokines is related to the efficacy of BCG [9-10]. By analyzing together the changes in some of these cytokines due to treatment with BCG, a nomogram predicting the efficacy of BCG was constructed using of 9 out of 12 selected cytokines [11]. Although data for this are lacking, part of the side effects may be related to the power of the immune response of the patient. In elderly patients, immunosenescence (the decreased capacity for generating an adequate immune response due to age [12,13]) may lead to a less pronounced cytokine induction and subsequent a less severe *local* side effects profile.

Nonetheless, when only local side effects were concerned, no difference related to age was observed.

There are several limitations of this study. Although the data for this analysis were prospectively collected and 487 patients were included in the main analyses, the comparison of the duration of treatment by age in the patients who stopped due to toxicity has limited power since 99 patients stopped due to toxicity and only 34 were > 70 years of age. Although this study is one of the largest in BCG treated patients, the data have been collected in a time period when guidelines didn't yet recommend a reTUR in high risk NMIBC, video cystoscopy was not routinely used and additional techniques like photodynamic or narrow band imaging cystoscopy were not yet available. Without these surgical improvements, a higher recurrence rate could be expected in this study compared to today's practice. As recurrence as a reason for stopping treatment is a competing risk for toxicity as a reason for stopping treatment, this could have lowered the risk for stopping due to toxicity. However, we have previously shown that age is not a prognostic factor for time to recurrence in this study, so a possible lower risk for stopping due to toxicity because of recurrence is not age dependent [2]. Another limitation is the eligibility upper age limit of 85 years in this study. This may have limited the number of patients in the older age group. Only 3.5% of the patients were more than 80 years of age.

This study was done using the TICE® BCG strain. As other strains of BCG may show differences in efficacy, there could also be differences in toxicity if another strain had been used. As previously reported, the addition of INH to BCG did not reduce either the systemic or local side effects. In 11 patients in the BCG + INH group, INH (but not BCG) was stopped due to transient liver toxicity [14]. The distribution of patient age was similar in the BCG and BCG + INH treatment groups. Although more patients stopped treatment for toxicity in the BCG + INH group, 24.2% versus 16.6%, the overall conclusions for age did not change when the two treatment groups were analyzed separately. No information about the use of anti-coagulants

is available, which may have been used more frequently in older patients and thus be protective for side effects as was suggested by Heiner [5].

CONCLUSION

In the treatment debate for patients with intermediate or high-risk NMIBC, the efficacy of BCG must be balanced against its risk of toxicity. This study shows that toxicity in elderly patients is not a valid reason for omitting BCG treatment.

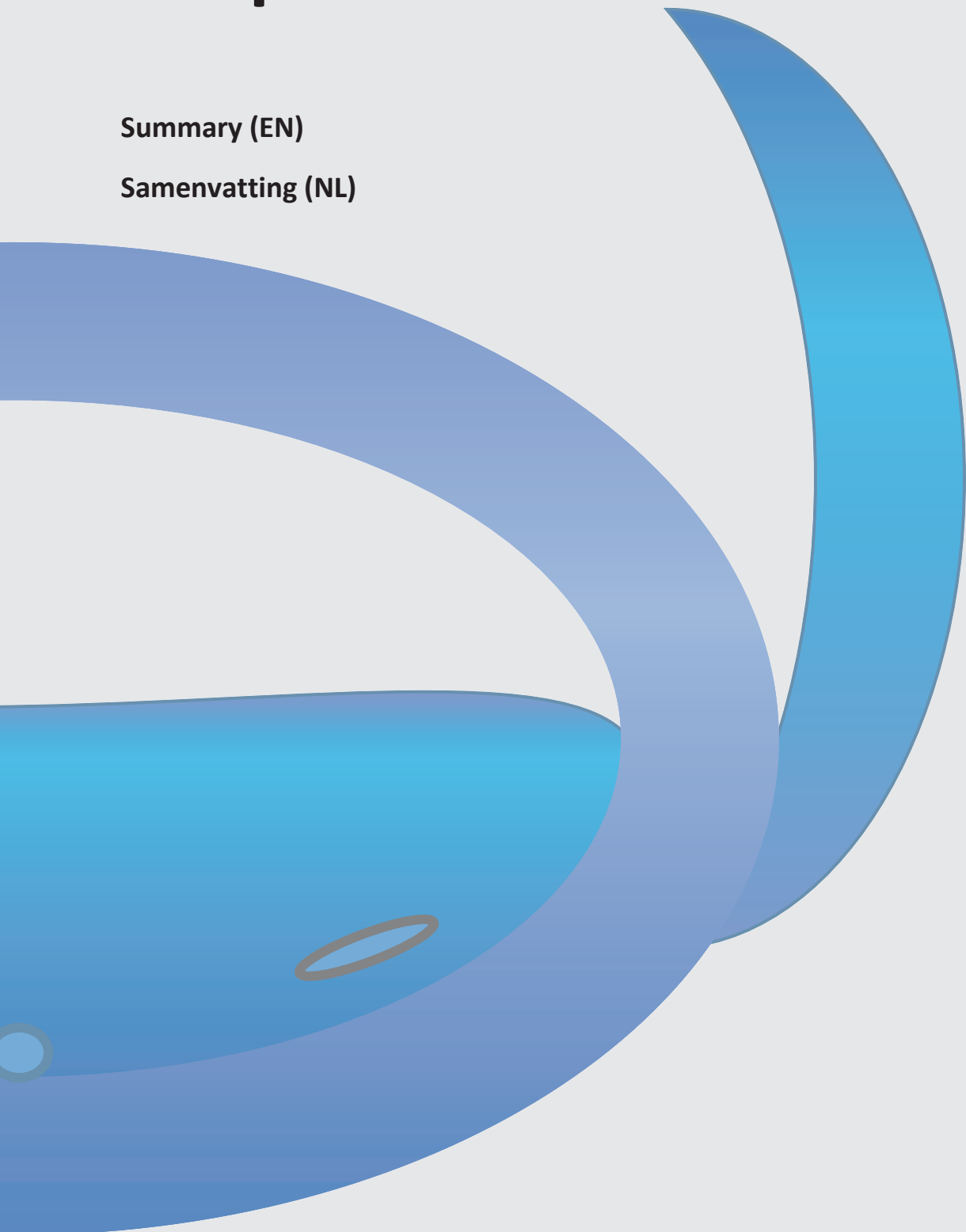
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Chapter 7

Summary (EN)

Samenvatting (NL)



SUMMARY (EN)

In the adjuvant treatment of non-muscle invasive bladder cancer, instillations with bacille Calmette-Guérin reduce the chance of recurrence of bladder cancer. This effect is especially valid when a schedule is used of 27 instillations over a period of 3 years. This scheme is build up by six weekly instillations, followed by 3 weekly instillations with an interval of 3 and afterwards 6 months of time. The adverse effects of BCG are a mayor disadvantage. They often occur and can be a reason to interrupt or even discontinue treatment.

Although it is possible to treat patients for these side effects if they remain after pausing treatment with tuberculostatic agents like isoniazid (INH), measures to prevent side effects are needed. By the the European Organization for Research and Treatment of Cancer Genito-Urinary group (EORTC-GU), trial 30911 was conducted in order to determine whether the combination of INH and BCG would decrease side effects as compared to BCG alone. Both study arms using BCG were compared to a third arm with treatment of the chemotherapeutic drug epirubicin. The initial and long term results were published in 2001 and 2010 respectively by Van der Meijden and Sylvester and showed no beneficial effect of INH on adverse effects and a significant lower recurrence rate in both BCG arms compared to the epirubicin arm.

Challenged by this result the EORTC-GU group designed Trial 30962, further focusing on reduction of adverse events. By reducing the delivered dose to 1/3, or by shortening the length of maintenance treatment from 3 years to 1 year, it was postulated that side effects could be reduced without compromising the efficacy.

In this thesis the final results on trial 30962 are presented, together with analyses done with the data of BCG treatment in trial 30911.

In **chapter 1**, the field of bladder cancer treatment is described. The difference between non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer is explained. Also the place of transurethral resection as important first step is discussed. A description of the role of adjuvant treatment with maintenance BCG in NMIBC is given.

In **part 1**, the focus is on efficacy of maintenance BCG treatment.

Chapter 2 presents the important final efficacy results of trial 30962. It described the analyses done and the conclusions in terms of efficacy results of the regime of dose reduction and shortening of the maintenance period. The study was designed to show no difference in efficacy, assuming that such a difference wasn't existing. However, due to a lower than expected event rate (there were less recurrences in the study population as expected beforehand), such a conclusion could not be drawn. Fortunately, we were able to draw some other important conclusions on the separate risk groups, showing that in intermediate risk patients treatment with normal dose BCG for a period of 1 year is sufficient. Furthermore, the reduced dose during 1 year was for both intermediate and high risk patients insufficient treatment. Finally, for high risk patients, full dose during 3 years was better compared to either 1 year or reduced dose.

Chapter 3 is focusing on efficacy results related to the age of patients. Because the life expectancy of the general population is increasing, the amount of older patients with NMIBC is increasing as well. The working mechanism of BCG is using the host's immune response. As in older people the quality of their immune response is lower compared to younger people, it is expected that BCG is less effective in the elderly. With the data set of trial 30911, we showed that older age is indeed related with a higher recurrence rate. Because in the study also epirubicin was tested, we concluded that although people older than 70 years of age had a worse prognosis compared to younger ones, BCG still is superior to epirubicin; also in the elderly.

In **chapter 4** the results on efficacy of BCG maintenance treatment of both trials were used in order to investigate prognostic factors in NMIBC patients treated with BCG. We were able to do this analysis in a large data set containing 1812 patients. We identified by multivariable analyses the following prognostic factors for recurrence: prior recurrence rate and number of tumors. For progression and death: tumor stage and grade. Patients with T1G3 showed the highest 1 and 5 years progression rate: 11.4% and 19.8% respectively. Disease specific death rates for this group at 1 and 5 years were 4.8% and 11.3% respectively. With these data we were able to create a nomogram predicting overall survival when treated with maintenance BCG.

In **part 2**, side effects of maintenance BCG are discussed.

Chapter 5 gives the results of side effect analysis of trial 30962. We present the amount and severity of side effects. Trial 30962 tried to find a way of reducing side effects by decreasing treatment time or dose. In the groups with reduced dose, the same amount of side effects was reported compared with full dose. It was also shown that effects were most prominent within the first year of treatment without a significant contribution of prolonged maintenance to 3 years.

In **chapter 6** we investigated the effect of age on the occurrence of side effects. In the data set of trial 30911, side effects that resulted in stopping treatment definitively, were linked to patients age. In this analysis we weren't able to show a relation between age and stopping treatment due to side effects. We concluded that older age is not a valid reason for omitting BCG to patients by the fear of more intense side effects.

SAMENVATTING (NL)

Bij de behandeling van niet-spierinvasieve blaaskanker (NMIBC) reduceren blaasspoelingen met bacille Calmette-Guérin (BCG) de kans op de terugkeer van blaaskanker. Dit effect is het grootst wanneer een schema wordt gehanteerd van 27 spoelingen gedurende 3 jaar. Dit onderhoudsschema bestaat uit een cyclus van 6 wekelijkse spoelingen, gevolgd door 3 wekelijkse spoelingen die eerst om de 3 en later om de 6 maanden worden gegeven. Een groot nadeel van BCG is de kans op neveneffecten: deze is vrij groot en kan dan leiden tot het moeten onderbreken of stoppen van de behandeling.

Het is weliswaar mogelijk om de neveneffecten te behandelen met tuberculostatika zoals isoniazide (INH) indien patiënten ondanks het staken van de behandelingen toch symptomen blijven houden, maar maatregelen die neveneffecten kunnen voorkomen zijn uiterst welkom. Trial 30911 van de European Organization for Research and Treatment of Cancer Genito-Urinary group (EORTC-GU groep), was erop gericht om te onderzoeken of de het geven van INH tijdens de behandeling met BCG het aantal neveneffecten zou doen afnemen, in vergelijking met de behandeling met BCG alleen. De beide studie armen waarin BCG werd gebruikt, werden vergeleken met een derde arm waarin het chemotherapeutikum epirubicine werd gebruikt. De eerste en de lange termijn resultaten van deze studie werden respectievelijk in 2001 en 2010 gepubliceerd door Van der Meijden en Sylvester en lieten geen voordeel zien van het toevoegen van INH aan de behandeling met BCG in het optreden van neveneffecten en daarnaast een significant kleinere kans op ziekte terugkeer in de beide BCG studie-armen in vergelijking met epirubicine.

Als gevolg van deze uitkomst ontwierp de EORTC-GU groep Trial 30962, die verder inzoomt op het terugdringen van neveneffecten. Nu door de gebruikte BCG dosis tot 1/3 te verlagen en/of de behandelduur te verkorten van 3 tot 1 jaar. De aanname bij deze studie was dat deze aanpassingen het optreden van neveneffecten kon terugdringen zonder de effectiviteit van de behandeling nadelig te beïnvloeden.

In dit proefschrift worden de resultaten van trial 30962 gepresenteerd en tevens aanvullende onderzoeken die uitgevoerd zijn met de gegevens van trial 30911.

In **hoofdstuk 1** wordt een overzicht gegeven van de behandeling van blaaskanker. Het verschil tussen niet-spierinvasieve blaaskanker en spierinvasieve blaaskanker is uitgelegd, samen met de rol van de trans-urethrale (blaas)tumor-resectie (TUR-T-operatie) als belangrijke eerste stap in de analyse en behandeling. Ook wordt de rol van aanvullende blaasspoelingen beschreven.

In **deel 1** wordt aandacht besteed aan de effectiviteit van een onderhoudsschema met BCG.

Hoofdstuk 2 geeft de resultaten weer ten aanzien van de effectiviteit van de behandeling zoals deze in trial 30962 bleek. We beschrijven welke analyses hiervoor zijn uitgevoerd en wat de conclusies zijn ten aanzien van de effectiviteit van de behandeling indien de dosis wordt gereduceerd of het interval van een onderhoudsbehandeling met BCG wordt verkort. Het ontwerp van de studie was erop gericht dat aangetoond zou kunnen worden dat er geen

verschil in effectiviteit tussen de behandelde groepen zou zijn. Gaandeweg de studie bleek echter dat het aantal patiënten dat recidieven van blaaskanker kreeg in de gehele studie lager uit viel dan van tevoren was ingeschat, wat ertoe leidde dat een harde conclusie over het al dan niet even goed zijn van de behandelingen in het algemeen toch niet getrokken mocht worden. Gelukkig bleken we met alle verzamelde gegevens wel in staat een aantal andere conclusies te trekken. Deze waren geldig voor de verschillende risicogroepen van patiënten ten aanzien van de kans op terugkeer van blaaskanker. We lieten zien dat voor de patiënten met een intermediair risico, de behandeling met een normale dosis BCG gedurende 1 jaar goed is en niet nog 2 jaar langer hoeft te duren. Ook bleek de gereduceerde dosis gedurende 1 jaar voor alle risicogroepen onvoldoende te zijn. En ten slotte dat voor de hoog-risicopatiënten de volledige dosis gedurende 3 jaar de beste behandeling is.

Hoofdstuk 3 behandelt de resultaten van een studie naar de effectiviteit van BCG in oudere patiënten. De levensverwachting van de gehele bevolking wordt steeds hoger en daarmee stijgt ook het aantal oudere patiënten met NMIBC. Het effect van BCG verloopt via activatie van het afweersysteem. Omdat bij oudere patiënten het afweersysteem minder goed functioneert dan bij jongere mensen, ligt het in de lijn der verwachting dat het effect van BCG afneemt naarmate de patiënt ouder is. Met behulp van de gegevens uit trial 30911 toonden we inderdaad aan dat de kans op terugkeer van blaaskanker in oudere patiënten die behandeld worden met BCG groter is dan in jongere patiënten, waarbij overigens ook bleek dat in deze groep ouder dan 70 jaar BCG toch nog beter werkte dan epirubicine.

In **hoofdstuk 4** worden de resultaten van de effectiviteit van BCG zoals die uit beide studies naar voren kwamen gebruikt om na te gaan welke prognostische factoren er zijn bij patiënten met NMIBC die behandeld worden met BCG. Met gegevens van 1812 patiënten konden we door middel van multivariabele analyses diverse prognostische factoren vaststellen. Voor de kans op terugkeer van blaaskanker waren dat: het aantal eerdere keren dat blaaskanker was opgetreden en het aantal blaastumoren. Voor de kans dat de blaaskanker voortschrijdt of leidt tot overlijden waren dat: het tumor stadium en de tumorgraad. Patiënten met een T1G3 tumor lieten de hoogste kans op voortschrijding zien na 1 en na 5 jaar van respectievelijk 11,4% en 19,8%. De aan de ziekte gerelateerde kans om te overlijden na 1 en 5 jaar waren voor deze groep respectievelijk 4,8% en 11,3%. Met behulp van deze gegevens creëerden we een nomogram die de algehele overlevingskans kan voorspellen van patiënten die met onderhouds-BCG worden behandeld.

In **deel 2** van het proefschrift wordt stilgestaan bij de neveneffecten van de behandeling met onderhouds-BCG.

In **hoofdstuk 5** worden de aantallen en soorten neveneffecten beschreven zoals die werden gerapporteerd in trial 30962. De studie was erop gericht om met een gereduceerde dosis of een korter behandelingschema het aantal neveneffecten terug te dringen. In de groep die

behandeld werd met een gereduceerde dosis bleek het aantal neveneffecten niet te verschillen ten opzichte van de groep die met de volledige dosis werd behandeld. Omdat de meeste neveneffecten al in het eerste jaar van de behandeling optraden, leidde het geven van meer dan 1 jaar BCG niet tot duidelijk meer gerapporteerde neveneffecten in deze periode.

Hoofdstuk 6 beschrijft het onderzoek naar het mogelijke effect van de leeftijd op de kans op het optreden van neveneffecten. Op basis van de gegevens van trial 30911 keken we hoe vaak neveneffecten leidden tot voortijdig staken van de behandeling en of dit gerelateerd was aan de leeftijd van de patiënt. We concluderen dat BCG niet vaker door neveneffecten gestaakt wordt op oudere leeftijd dan op jongere leeftijd en dat oudere leeftijd mede daardoor geen extra reden is de behandeling niet aan te bieden.

Chapter 8

Future perspectives



FUTURE PERSPECTIVES

BCG in a maintenance schedule is the most investigated compound so far as adjuvant treatment of intermediate- to high risk bladder cancer and has proven to be one of the most effective drugs to prevent recurrences. Information about the most appropriate treatment schedule for intermediate and high risk NMIBC derived from trial 30962 [Chapter 2] are adopted into the EAU guidelines on non muscle invasive bladder cancer (NMIBC): it is advised to treat patients at high risk with 3 years, full dose, in contrast with patients with intermediate risk, who can safely omit treatment after 1 year [1]. The latter includes patients with recurrent disease despite chemotherapeutic instillations who may well benefit from BCG. Also the conclusions of chapter 3, that BCG is less effective in patients > 70 years of age but still more than epirubicin is adopted by these guidelines. We can state that the research presented in this thesis is in this way already valorized.

However, 3 aspects of maintenance BCG are bothersome:

- (1) The side effects of the treatment are frequently seen (62,8%) and have implications for the patients, regularly leading to discontinuation of the treatment (7,8%) [Chapter 5].
- (2) The recurrence and progression despite maintenance BCG: we confirmed that patients with T1G3 do the worst with a 5 years' progression rate of nearly 20% [chapter 4]. For these patients, other strategies are mandatory.
- (3) The world-wide and long lasting production problem leading to a shortage of BCG.

All of the above mentioned aspects demand alternative adjuvant treatment options for patients with intermediate to high risk NMIBC.

One of the most effective alternative treatments for very high risk patients is a cystectomy with subsequent creation of a bladder substitute (ilial conduit or neobladder). Other less rigorous strategies use other or a combination of compounds as bladder instillations and/or device assisted chemotherapeutic instillations. In this respect, promising data are available on the use of gemcitabine, Radiofrequency-Induced Thermo-chemotherapy (RITE) with mitomycin-C (MMC), and Electromotive drug administration (EMDA) with MMC combined with BCG.

THE ROLE OF EARLY CYSTECTOMY AND SELECTION TOOLS FOR THIS APPROACH

In very high risk cases (large or multifocal T1G3 tumors, recurrent T1G3 tumors or combined with CIS) it is advised to discuss the option of early cystectomy with the patient, according to the European guidelines of NMIBC [1]. Within the group of recurrent patients some progress to muscle invasive bladder cancer, making a cystectomy the gold standard therapy [2]. For these patients, prognosis is worse compared to primary muscle invasive bladder cancer (MIBC) as was first described by Schrier et al. [3]. This underlines again that we urgently need a thorough tool in order to make a proper and timely selection of patients for this intensive surgical approach. Could bladder cancer markers be used for this? Several markers that give information about bladder cancer recurrence have been developed. However, even for this

purpose none of the urinary markers were able to do better than cystoscopy and cytology in diagnosing recurrent disease [4]. For example, a recently tested marker in bladder cancer patients, urinary tyrosine-phosphorylated proteins, showed a sensitivity of 80% and a specificity of 79% for the presence of bladder cancer using a certain cut-off level compared to healthy people. [5]. This results are comparable with other available urinary tests [6]. Combining several tests may improve the sensitivity and specificity. For example, by combining epithelial membrane antigen (EMA) and nuclear matrix protein 52 (NMP-52), the sensitivity and specificity increased to 94% and 80%, respectively [7]. Nevertheless, the ultimate goal in creating and testing panels of markers will not only be predicting a recurrence but prognosticate progression despite adjuvant treatment. For this purpose, marker panels aren't available yet. In this respect, some attention may go to circulating tumor cells (CTC). These have been linked to metastatic MIBC, but in 6 of 16 of patients with T1 non metastatic disease, CTC were also present [8].

GEMCITABINE

Although BCG is superior to the mostly used chemotherapeutic agents MMC and epirubicin, in the past years another chemotherapeutic drug has been tested as adjuvant treatment in NMIBC. In a randomized phase 2 study patients recurring after BCG treatment were treated with Gemcitabine 2000mg in 50-100 cc NaCl,9%. The results showed a recurrence rate comparable with initial BCG treatment with acceptable side effects. Several schemes were used. An example is the schedule used by Di Lorenzo et al, who studied bi-weekly instillations of 2000mg Gemcitabine in 50 ml during in 6 weeks, followed by 3 weekly instillations after 3, 6 and 12 months [9]. Another example is derived from a phase 2 trial by Skinner, that used a scheme of Gemcitabine 2000mg/ 100 ml of once a week during 6 weeks, followed by 10 monthly instillations [10]. Despite these positive results and the need for an alternative for BCG, no registration studies are conducted currently. In October 2014, the Dutch Urology Association sent out a communication and advised it as alternative treatment in case of BCG shortage [11]. In 2015, Mostafid et al. published a comparable advice [12].

DEVICE ASSISTED CHEMOTHERAPEUTIC INSTILLATIONS

The superior effect of RITE compared to MMC was initially shown by Colombo [13]. The report on a randomized phase 3 trial on BCG vs. RITE in intermediate and high risk NMIBC patients is submitted. An abstract on this study showed that RITE resulted in a lower RFS, at least in intermediate risk NMIBC patients compared to BCG in a maintenance schedule of 1 year [14]. By creating a field of electrical current inside the bladder using a surface electrode at the abdominal wall and an electrode inside the bladder, EMDA causes iontophoresis which causes a more thorough penetration of MMC inside the bladder mucosa. In a study by Di Stasi this instillation technique was combined with BCG instillations that were given alternately and gave a higher disease free interval by the combination as compared to 1 year of maintenance BCG alone in high risk patients [15].

MYCOBACTERIAL CELL WALL PARTICLES

A potentially promising development is the isolation of surface proteins of Mycobacteria. Derived from BCG, cell wall skeleton (CWS), showed a negative response on viability of bladder cancer cells in vitro [16]. In animal studies using CWS, the effect was only seen when the particles were packed inside liposomes [17]. This strategy, that still demands BCG as a compound, could lower side effects, especially the risk of BCG sepsis but is no answer for recurrence rates or BCG shortage. Another approach is by the use of cell wall parts of Mycobacterium phlei. In 2015 Morales et al. published a phase 2 study in high risk patients who relapsed on BCG. The disease free rate at 2 years was 19%. Side effects were mild and mainly local [18].

REDUCING BCG DOSE ON INDICATION OF SIDE EFFECTS

In trial 30962, reduction of the dose to 1/3 was investigated in a randomized fashion. This led to the conclusion that in high risk patients this was insufficient treatment [chapter2]. On the other hand, it was not confirmed that a reduced dose led to significantly less side effects [chapter 5]. What we do not know is the effect of reducing the dose only in patients that are experiencing side effects. When side effects otherwise would have resulted in a complete stop of the treatment, continuing with 1/3 dose can be considered after a clear and open discussion with the patient about the pro-'s and con's.

BCG FAILURE IN INTERMEDIATE RISK PATIENTS

Despite BCG maintenance therapy in intermediate risk patients, recurrent disease will occur in 5-20 percent of patients [chapter4]. The EAU guidelines on NMIBC give the advice to either repeat BCG, to start chemotherapeutic instillations or to do a cystectomy. Because maintenance BCG is superior to chemotherapeutic instillations in all RCT's, it seems logical to upscale treatment to cystectomy unless the patient is not fit for this extensive surgery. However, on an individual basis, some patients can react poorly on BCG while reacting very well on e.g. MMC. Aspects of time to first recurrence, multiplicity and size of tumor recurrence and the quality of the transurethral resection has to be weighted against the impact of a cystectomy on the quality of life of the individual patient.

IMPROVEMENTS IN RESECTION OF BLADDER TUMORS

The expected recurrence rates in the treatment arms of trial 30962 [chapter2] were initially estimated at a higher level than eventually appeared during the lead time of the study. This resulted in less events as defined in the protocol when finally closing the trial. One of the factors that may have contributed to the lower recurrence rate could be the improvement in visualisation leading to better transurethral resections. In the past 20 years, video cystoscopy has replaced direct cystoscopy, both in the outpatient clinic as in the operation theatre. Further improvements in video resolution to High Definition (HD) are expected to add to the accuracy although no research is done to evaluate this. Other technical improvements in cystoscopy include the introduction of photodynamic diagnostics (PDD). This technique uses

aminolevulinic acid that binds to cells that leads to the accumulation of fluorescent porphyrines. With the ability to use a blue light source (380-470nm wavelength) and a computer that compensates the low luminous efficacy, altered tissue can be recognised and resected [19]. Another application of a filtered light source is Narrow Band Imaging (NBI). By using only blue and green light (excluding red), blood vessels will become black. Altered patterns of vessels can be recognized easier, leading to an improved resection rate of cancerous tissue [20]. Both techniques will stimulate the urologist to do a thorough inspection of the bladder wall before starting the resection. This aspect is suggested to be an important factor for better resection, as discussed in the study by O'Brien et al. that showed equally well results in white light resections as well some time after implementation of PDD [21].

A CLOUDY FUTURE?

In searching for better treatment of NMIBC one aspect is easily overlooked. All efforts in solving an existing disease could be redundant if bladder cancer prevalence will drop dramatically. One of the most important risk factors is cigarette smoking. This habit leads to a relative risk (RR) of developing bladder cancer of 3.49 and a RR of dying from bladder cancer of 1.48 for current smokers [22]. In the policy to discourage cigarette smoking by warnings on the packages, bladder cancer is not mentioned at all. By informing potential patients and prohibiting smoking a significant reduction of bladder cancer can be established, potentially reducing bladder cancer burden far more efficient than by the discussed adjuvant treatments.

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CURRICULUM VITAE

Jorg Oddens was born at the 27th of march, 1969, in Doetinchem, The Netherlands and moved together with his parents (Dr. D.A.M. Oddens and J.J.M. Oddens-Putman) and his brother (Dr. B.J. Oddens) several times within the country. After finishing Gymnasium β at the Rijksscholengemeenschap in Tiel he moved to Rotterdam to start medical school at Erasmus University. In the third year of his study he started as assistant-nurse at the Thoracic surgery ward of the Erasmus Medical Center. The research training at the end of the study was also done at this department and lead to his first publication. Awaiting the start of his internships, he worked at the Anatomical Laboratory at the University Leiden and helped to describe embryonic stem cells that contribute to the formation of coronary arteries. After finishing medical school, he served 1 year as a resident of the thoracic surgery department of the University Medical Centre Utrecht (UMCU). He then started a project at the same hospital to build a Pelvic Floor Disease center, a collaboration of the surgical, urological and gynecological departments. Hereafter, he switched to urology and qualified as a resident in training for urology. In 2000 he started his general surgery training at the Bosch Medicentrum, 's-Hertogenbosch (Dr. J. Wever). In the same hospital, he was trained for another two years at the urology department (Dr. J.W. Hoekstra). The academic training was at the UMCU (Dr. R.J.A. van Moorselaar, Prof. dr. J.L.H.R. Bosch). During his residency at the Bosch Medicentrum he was introduced to the EORTC-GU group meetings by Dr. A.P.M. van der Meijden, who was at that time project leader of trial 30962. This appeared to be the very first act that eventually lead to participating in the research that is now summarized in this thesis.

As a urologist he was further trained in oncological urology for 6 months at the Antonie van Leeuwenhoek Hospital in Amsterdam (Prof. dr. S. Horenblas). Since 2006 he is part of an ambitious team of urologists, together with E.S.S. van de Aker, Dr. H.P. Beerlage, P. van Migem, R.A. Schipper, Dr. B.Ph. Schrier and A.M.A. de Vylder at the department of urology of the Jeroen Bosch Hospital, 's-Hertogenbosch.

In 2000 he married his girlfriend Ilone de Bruijn. In the same year she gave birth to their first son Wessel and in 2004 to their second son Reimer. They live in the city center of 's-Hertogenbosch, The Netherlands.

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