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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 Genito-Urinary 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 (NMIBC), its efficacy in older patients is controversial.
Objective: To determine the effect of age on prognosis and treatment outcome in patients with stage Ta T1 NMIBC treated with maintenance BCG.
Design, setting, and participants: A total of 957 patients with intermediate- or high-risk Ta T1 (without carcinoma in situ) NMIBC were randomized in European Organization for Research and Treatment of Cancer (EORTC) trial 30911 comparing six weekly instillations of epirubicin, BCG, and BCG plus isoniazid followed by three weekly maintenance instillations over 3 yr.
Outcome measurements and statistical analysis: Cox multivariate proportional hazards regression models were used to assess the relative importance of age for recurrence, progression, overall survival, and NMIBC-specific survival with adjustment for EORTC risk scores.
Results and limitations: Overall, 822 eligible patients were included: 546 patients in the BCG with or without INH arms and 276 in the epirubicin arm. In patients treated with BCG with or without INH, 34.1% were >70 yr of age and 3.7% were >80 yr. With a median follow-up of 9.2 yr, patients >70 yr had a shorter time to progression ($p = 0.028$), overall survival ($p < 0.001$), and NMIBC-specific survival ($p = 0.049$) after adjustment for EORTC risk scores in the multivariate analysis. The time to recurrence was similar compared with the younger patients. BCG was more effective than epirubicin for all four end points considered, and there was no evidence that BCG was any less effective compared with epirubicin in patients >70 yr.
Conclusions: In intermediate- and high-risk Ta T1 urothelial bladder cancer patients treated with BCG, patients >70 yr of age have a worse long-term prognosis; however, BCG is more effective than epirubicin independent of patient age.
Patient summary: Intravesical bacillus Calmette-Guérin for non–muscle-invasive bladder cancer is less effective in patients >70 yr of age, but it is still more effective than epirubicin.
Trial registration: This study was registered with the US National Cancer Institute clinical trials database (protocol ID: EORTC 30911; http://www.cancer.gov/clinicaltrials/search/view?cdrid=77075&version=HealthProfessional&protocolsearchid=12442243#StudyIdInfo_CDR0000077075).

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1. 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 European Organization for Research and Treatment of Cancer (EORTC) risk tables can be used [1,2]. After transurethral resection of bladder tumor, preferably followed by an immediate postoperative instillation and pathologic confirmation of the stage and grade of the disease, adjuvant intravesical instillations are recommended in the intermediate- and high-risk groups, with bacillus Calmette-Guérin (BCG) 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 with chemotherapeutic agents prevents it from being recommended in all patients with NMIBC [2,8,9]. Therefore, in daily practice, it is only in high-risk 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, T-helper cells, T cells, and natural killer cells, is seen. These immunologic responses also lead to an elevation of cytokines in urine [10].

The part of the massive immunogenic cascade triggered by BCG that is responsible for its antitumor 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 interleukin (IL)-2 measured in urine samples during the induction course [11,12].

It is therefore likely that individual differences in immunologic 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. It had already been shown in the 1970s that immune responses, especially T-cell–mediated responses, were significantly depressed in healthy people >60 yr of age compared with a control group <25 yr 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 immunologic response to the vaccine, resulting in 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 Surveillance Epidemiology and End Results database were >65 yr of age [15].

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 the EORTC trial 30911, which compared epirubicin, BCG, and BCG plus isoniazid (INH) followed by maintenance instillations for 36 mo [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 with the results obtained with epirubicin in both the younger and older patients.

2. Materials and methods

From January 1992 to February 1997, 957 patients with intermediate-risk 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 1–3, histologic-proven urothelial bladder cancer were included. Exclusion criteria were a primary solitary tumor, muscle-invasive tumor, or carcinoma in situ; patient age >85 yr; a World Health Organization performance status 3 or 4; previous treatment with doxorubicin, epirubicin, or BCG; and intravesical treatment during the previous 3 mo. Tumors were classified according to the 1992 TNM classification of the International Union against Cancer [16].

Within 24 h after transurethral resection (TUR), before receiving the definitive histology report, patients were randomized to one of three adjuvant treatment arms: epirubicin weekly for 6 consecutive weeks starting within 24 h after TUR or BCG with or without INH weekly for 6 consecutive weeks starting 7–15 d after TUR. 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 3 mo during the first 3 yr and every 6 mo thereafter. In case of a suspected recurrence, pathologic confirmation by a TUR was mandatory. The primary end point was the time to first bladder recurrence with secondary end points 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 were previously published [7,8].

To determine the prognostic importance of age in patients treated with BCG and to compare the outcome with BCG with the results obtained with epirubicin in both the younger and older patients, Cox univariate and multivariate proportional hazards regression models were fit with end points 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: ≤70 yr and >70 yr 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 scores (0–17) and recoded progression scores (0–6, 7–13, 14–23) [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 to take into account patients who may have died before the event of interest (competing risk) except for overall survival that was estimated using Kaplan-Meier curves.

3. 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 with or without INH arms and 276 patients in the epirubicin arm, used as a reference group.

Table 1 provides the distribution of age along with other patient characteristics. In the 546 patients treated with maintenance BCG with or without INH, 360 (65.9%) were ≤70 yr of age; 34.1% were >70 yr. Only 20 patients (3.7%) were >80 yr. Table 2 reflects the distribution of age according to the EORTC recurrence and progression scores in BCG patients, and Supplemental Table 1 provides patient outcome according to treatment group for the various end points.

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

Based on a median duration of follow-up of 9.2 yr, there was not a significant effect of age on time to recurrence in patients receiving BCG (Table 3; Fig. 1). However, in both the univariate and multivariate analyses, BCG patients >70 yr had a significantly shorter time to progression (Table 3; Fig. 2), overall survival (Table 3; Supplemental Fig. 1), and NMIBC-specific survival (Table 3; Fig. 3) than BCG patients ≤70 yr. 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 end points previously considered, forest plots in Figure 4a–4d show the benefit of BCG compared with epirubicin in the two age groups, with similar reductions in the event rate on BCG in both age groups for all four end points.

Table 1 – Distribution of patient characteristics according to treatment

Patient characteristics	Treatment		
	BCG with or without INH (n = 546) n (%)	Epirubicin (n = 276) n (%)	Total (n = 822) n (%)
Age, yr			
≤60	146 (26.7)	74 (26.8)	220 (26.8)
61–70	214 (39.2)	100 (36.2)	314 (38.2)
71–80	166 (30.4)	90 (32.6)	256 (31.1)
>80	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)
Recurrence ≤1/yr	145 (26.6)	61 (22.1)	206 (25.1)
Recurrence >1/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)
No. 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)
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)

BCG = bacillus Calmette-Guérin; INH = isoniazid; WHO = World Health Organization.

4. 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 outcomes, 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 2 trial in which 1106 patients were treated with BCG combined with interferon-α in a maintenance scheme of 1 yr, age >80 yr compared with patients 61–70 yr was indeed an independent negative predictor of cancer-free survival with an adjusted hazard ratio of 1.564 (CI 95%; 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 report, age >70 yr was a prognostic factor with regard to recurrence [18]. In the other, advanced age (≥75 yr) was associated with a higher progression rate [20].

Table 2 – Distribution of age according to EORTC recurrence and progression scores in bacillus Calmette-Guérin patients

Age distribution by EORTC scores					
	Age				
	≤60 yr (n = 146) n (%)	61–70 yr (n = 214) n (%)	71–80 yr (n = 166) n (%)	>80 yr (n = 20) n (%)	Total (n = 546) 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)

EORTC = European Organization for Research and Treatment of Cancer.

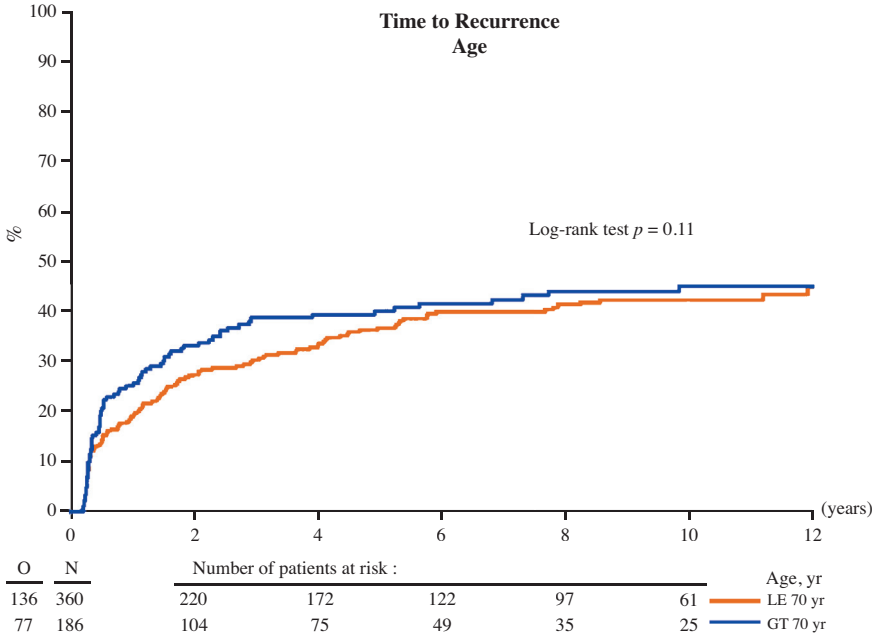

Fig. 1 – Distribution of patient characteristics according to treatment. O = observed number of events, N = number of subjects, LE = aged ≤70 yr; GT = aged >70 yr.

In the current study, age >70 yr was also found to be a negative factor for the prognosis of patients treated with maintenance BCG with respect to time to progression, overall survival, and NMIBC 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. However, a limitation of our study is the upper age limit of 85 yr, which reduced the number of patients in the older age group.

Club Urological Español de Tratamiento Oncológico, which used a scheme of 12 BCG instillations for 5 mo, compared with the current report involving a true maintenance scheme of 36 instillations for 3 yr, found age >60 yr 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 >70 yr 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 immunologic response to full-dose BCG may be much stronger than necessary for an adequate antitumor 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,

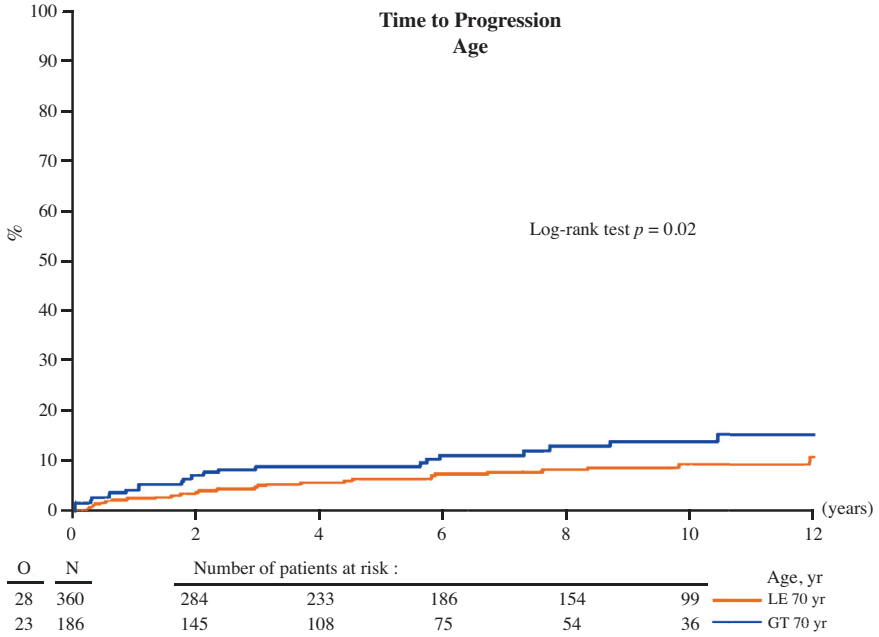

Fig. 2 – Time to progression in bacillus Calmette-Guérin patients by age group. O = observed number of events, N = number of subjects, LE = aged ≤70 yr; GT = aged >70 yr.

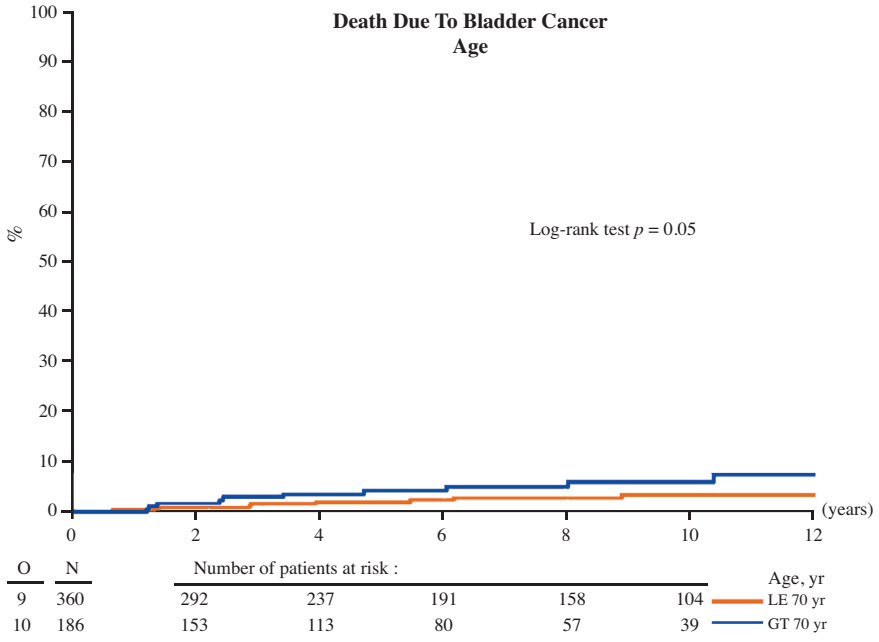

Fig. 3 – Bladder cancer–specific mortality of bacillus Calmette-Guérin patients by age group. O = observed number of events, N = number of subjects, LE = aged ≤70 yr; GT = aged >70 yr.

although recent data suggest that full-dose BCG is more effective than a one-third or one-quarter dose of 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 with 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 yr, 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

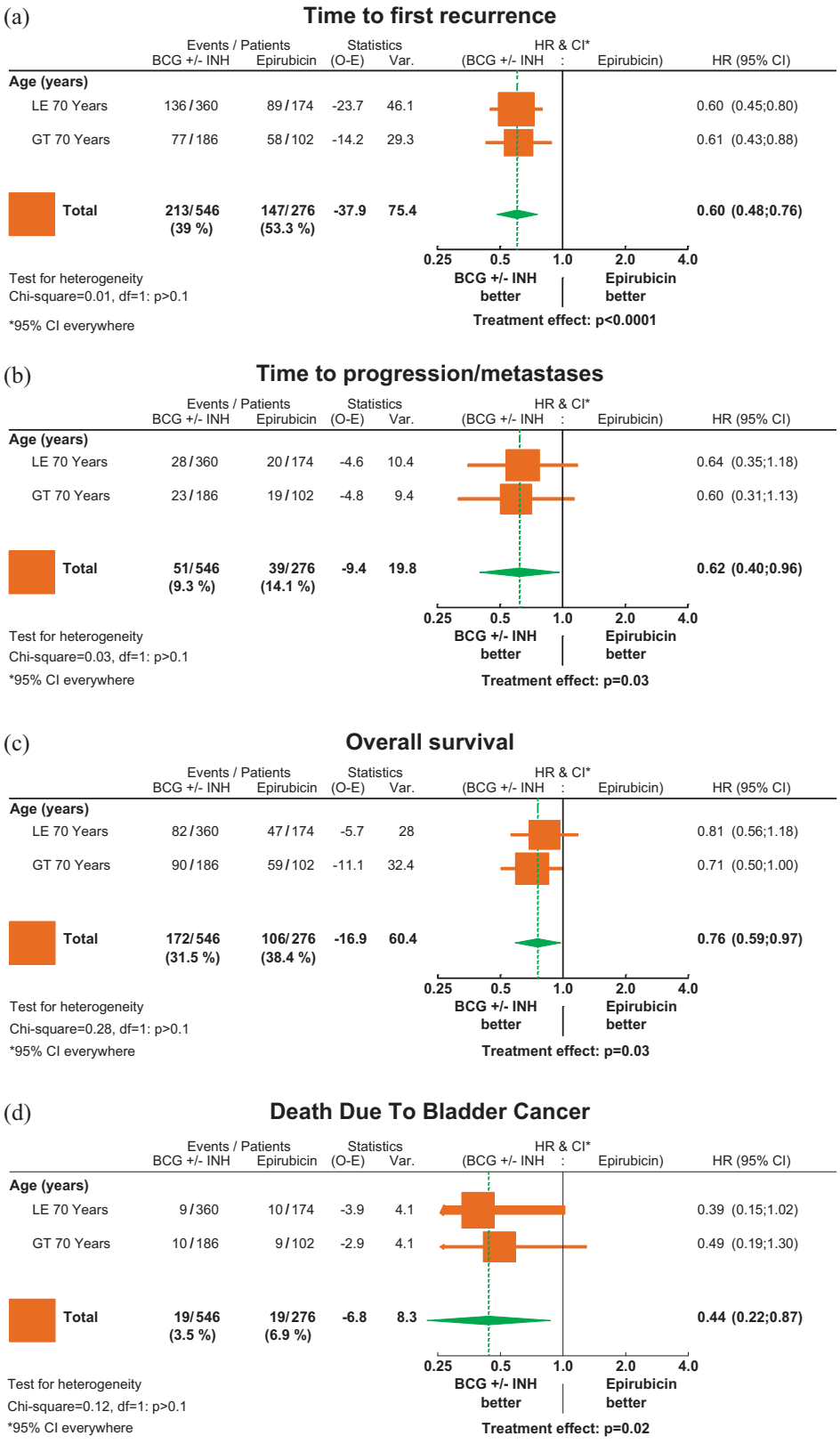

Fig. 4 – (a) Time to first recurrence; (b) time to progression; (c) duration of survival; (d) bladder cancer–specific mortality. LE = aged ≤70 yr; GT = aged >70 yr.

Table 3 – Univariate and EORTC risk score adjusted effect of age in bacillus Calmette-Guérin patients

	Recurrence		Progression		Overall survival		Death from bladder cancer	
Univariate	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, yr								
≤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
	Recurrence*		Progression**		Overall survival**		Death from bladder cancer**	
Multivariate	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, yr								
≤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

CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; HR = hazard ratio.
* Adjusted for EORTC recurrence score (0–17).
** Adjusted for recoded EORTC progression score (0–6, 7–13, 14–23).

guidelines. The results of this study are thus expected to be valid in current-day practice.

5. Conclusions

In intermediate- and high-risk stage Ta T1 urothelial bladder cancer patients who receive BCG, BCG is less effective in patients >70 yr of age in terms of time to progression, overall survival, and NMIBC-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 end points considered.

Author contributions: Jorg Oddens had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Oddens, Sylvester.
Acquisition of data: Oddens, Brausi, Kirkels, van de Beek, van Andel, de Reijke, Prescott, Witjes, Oosterlinck.
Analysis and interpretation of data: Oddens, Sylvester.
Drafting of the manuscript: Oddens, Sylvester.
Critical revision of the manuscript for important intellectual content: Oddens, Sylvester, de Reijke, Prescott, Witjes, Oosterlinck.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2014.05.033.

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