EUROPEAN UROLOGY 70 (2016) 341–347

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Bladder Cancer

Intravesical Bacillus Calmette-Guérin Versus Combination of Epirubicin and Interferon-α2a in Reducing Recurrence of Non–Muscle-invasive Bladder Carcinoma: FinnBladder-6 Study

Timo Marttila [a,†,*], *Riikka Järvinen* [b,†], *Tapani Liukkonen* [c], *Erkki Rintala* [b], *Peter Boström* [d], *Marjo Seppänen* [e], *Teuvo Tammela* [f], *Pekka Hellström* [g], *Sirpa Aaltomaa* [h], *Markku Leskinen* [a], *Mika Raitanen* [a], *Eero Kaasinen* [i], *the FinnBladder Group*

[a] *Department of Urology, Seinäjoki Central Hospital, Seinäjoki, Finland;* [b] *Department of Urology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland;* [c] *Department of Surgery, Mikkeli Central Hospital, Mikkeli, Finland;* [d] *Department of Urology, Turku University Hospital, Turku, Finland;* [e] *Department of Surgery, Satakunta Central Hospital, Pori, Finland;* [f] *Department of Urology, Tampere University Hospital, Tampere, Finland;* [g] *Department of Urology, Oulu University Hospital, Oulu, Finland;* [h] *Department of Urology, Kuopio University Hospital, Kuopio, Finland;* [i] *Department of Surgery, Hyvinkää Hospital and Helsinki University Hospital, Hyvinkää, Finland*

Article info

Article history:
Accepted March 26, 2016

Associate Editor:
Stephen Boorjian

Keywords:
Bacillus Calmette-Guérin
Epirubicin
Instillation therapy
Interferon α-2b
Mitomycin C
Recurrent non–muscle-invasive bladder cancer
SWOG

Abstract

Background: Patients with non–muscle-invasive bladder cancer (NMIBC) belonging to the intermediate-risk group should be treated with intravesical instillations to prevent recurrence and progression.
Objective: We compared the outcome of a monthly maintenance bacillus Calmette-Guérin (BCG) regimen with that of epirubicin (EPI) and interferon-α2a (IFN) in patients with NMIBC.
Design, setting, and participants: Our prospective randomized multicenter study comprised 229 eligible patients with frequently recurrent TaT1 grade 1–2 or low-grade NMIBC enrolled between 1997 and 2008.
Interventions: The four-arm study involved a single perioperative instillation of EPI plus five weekly instillations of BCG or EPI/IFN, followed by 11 monthly instillations in the 1-yr BCG or EPI/IFN maintenance arms, further followed by four additional quarterly instillations in the two 2-yr maintenance arms.
Outcome measurements and statistical analysis: Time to recurrence, progression, disease-specific survival, and overall mortality were analyzed using the Kaplan-Meier and cumulative incidence analyses plus the Cox and proportional subdistribution hazards models.
Results and limitations: The median follow-up time was 7.5 and 7.4 yr in the BCG and EPI/IFN groups, respectively. The probability of recurrence was significantly lower in the BCG group than in the EPI/IFN group. The probability was 39% versus 72% at 7.4 yr, respectively (hazard ratio [HR]: 0.41; 95% confidence interval [CI], 0.28–0.60; $p < 0.001$). There was no significant difference in the probability of progression or in overall survival. However, there was a significant difference in disease-specific mortality in favor of the BCG group (HR: 0.20; 95% CI, 0.04–0.91; $p = 0.04$).
Conclusions: The monthly maintenance BCG regimen showed excellent efficacy and was significantly better in preventing recurrence than a similar regimen of EPI/IFN-α2a.

† These authors contributed equally.
* Corresponding author. Seinäjoki Central Hospital, Hanneksenrinne 7, 60220 Seinäjoki, Finland.
Tel. +358 6 4154111; Fax: +358 9 47178317.
E-mail address: timo.marttila@epshp.fi (T. Marttila).

http://dx.doi.org/10.1016/j.eururo.2016.03.034

Patient summary: A monthly bacillus Calmette-Guérin (BCG) regimen showed excellent efficacy and was significantly better in preventing recurrence than a similar regimen of epirubicin and interferon-α2a.
Trial registration: Registration was not considered necessary at this stage of the follow-up because the study was initiated as early as in 1997, before the current requirements concerning study registrations were implemented.

1. Introduction

Non–muscle-invasive bladder cancer (NMIBC) is a heterogeneous disease with a variable risk of recurrence and progression. The European Association of Urology guidelines panel recommends stratification of patients into three risk groups, according to which further instillation therapy is recommended [1]. For low-risk patients, the panel recommends only one single perioperative chemotherapy instillation. Treatment of intermediate-risk patients should further consist of adjuvant chemotherapy or bacillus Calmette-Guérin (BCG) instillations for 1 yr. Full-dose BCG therapy for 1–3 yr is warranted only for high-risk tumors. The 3-yr therapy stems from a regimen designed by SWOG [2]. The SWOG regimen consists of an induction period of six weekly instillations followed by three weekly BCG instillations given at 3 and 6 mo, and after that, every sixth month for up to 3 yr. Alternatively, the BCG maintenance therapy may comprise monthly BCG instillations. Ehdaie et al concluded in their review [3] that the optimal BCG schedule and duration of maintenance is unknown [4,5].

Epirubicin (EPI) and mitomycin (MMC) are widely used intravesical chemotherapy agents to prevent bladder cancer (BCa) recurrences [6]. Intravesical interferon (IFN) immunotherapy has been used as an adjunct to BCG in some trials [4,7,8]. Some promising results have also been reported on a well-tolerated combination of IFN and chemotherapy [9–12].

Although considered the most effective treatment, BCG immunotherapy causes many and even serious adverse events, and hence there is a need for better tolerated treatment options [1].

With these considerations in mind, the FinnBladder-6 study was launched to compare the efficacy and tolerability of EPI and IFN with a monthly BCG regimen in reducing the recurrence of NMIBC.

2. Patients and methods

Between 1997 and 2008, 272 patients with frequently recurring TaT1 grade 1–2 NMIBC were enrolled in the prospective randomized multicenter FinnBladder-6 study. Inclusion criteria were at least two histologically verified TaT1 grade 1–2 or low-grade recurrences during the previous 18 mo. In case of positive cytology, random biopsies were recommended. Patients had to have at least 6 mo since the possible previous instillation therapy. Central randomization was used. After verbal consent was obtained, a local investigator contacted the FinnBladder secretary who, based on a file list, allocated the patient to one of the four groups, with a confirmation made by fax. Although no stratification or blocking was used, the four groups would have been fully balanced if the goal of 300 randomizations had been met. The protocol was designed to fulfill the ethical requirements of the Helsinki Declaration and the ethical committees.

According to a protocol, all the patients were allocated to receive a single perioperative instillation of EPI 100 mg/100 ml (Farmorubicin; Pharmacia, Peapack, NJ, USA) within 2 h after transurethral resection of the bladder (TURB). Groups A1 and A2 were further treated with five induction instillations of BCG (5×10^8 CFU in 100 ml saline, OncoTICE 5×10^8 CFU; Organon Teknika, Durham, NC, USA), followed by either 1- or 2-yr maintenance. Groups B1 and B2 had a similar regimen comprising a combination of EPI 50 mg/50 ml and INF-α2a (9 mU/50 ml saline; Roferon; Roche, Basel, Switzerland) (Fig. 1).

Upper urinary tract tumors were excluded by radiologic and pathologic assessment. Patients were followed by cystoscopy and cytology every 3 mo during the first 2 yr, every 6 mo for the next 3 yr, and after that according to the discretion of the clinician. Upper urinary tract imaging was done if considered necessary.

The planned population of 300 patients enables detecting, taking into account patients lost to follow-up, an improvement of 15% from a recurrence-free probability of 50% (269 patients and 114 events) using a one-tailed test with an α value of 0.05 and a β value of 0.20.

The primary end point of the study was time to first recurrence. Secondary end points were time to progression, disease-specific (DS) mortality, and overall survival (OS).

Recurrence was defined as pathologically verified NMIBC TaT1 or carcinoma in situ (CIS). Definition of progression was a pathologic sample of T2 or higher disease. If progression was the first event without a preceding recurrence, it was calculated as a recurrence. The follow-up time was calculated from the day of randomization at TURB to the latest entry of patient reports or death. Calculations were done with the general public license statistical software R v.3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) including the survival and cmprsk package. The chi-square test, the unpaired *t* test, and the Mann-Whitney test were used to compare the patient characteristics between the groups.

Survival was analyzed using the Kaplan-Meier technique and the Cox proportional hazards model. The cumulative incidence analysis and the proportional subdistribution hazards model were used for testing the other end points as well as for testing the significance of potential explanatory variables. A p value ≤ 0.05 was considered statistically significant.

3. Results

Of the 272 allocated patients, 236 fulfilled the inclusion criteria, and 229 were ultimately eligible for the intention-to-treat analysis (Table 1 and Supplementary Fig. 1). Due to decreasing recruitment, the study was closed prematurely. Because the number of patients was too small for testing the difference between the 1- and 2-yr therapy and no tendency of further efficacy was observed from four additional instillations in the second year (Supplementary Fig. 2), the main analyses were made between the combined BCG

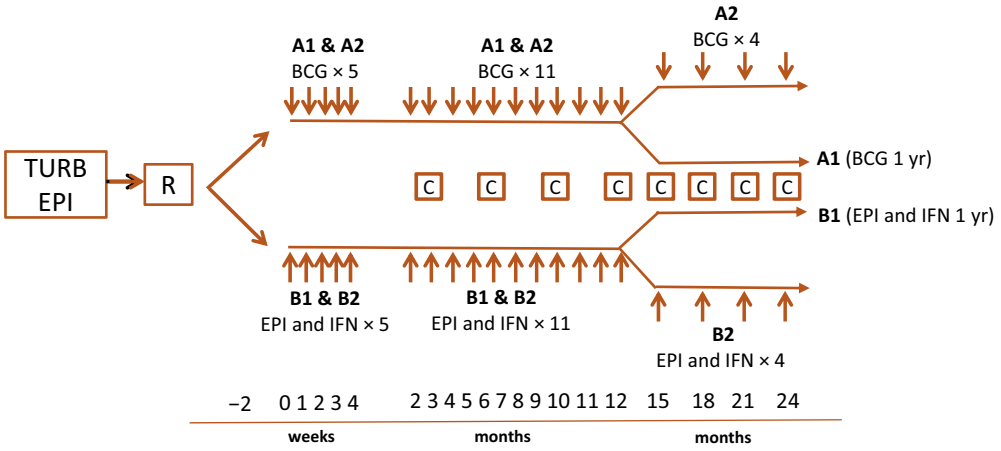


Fig. 1 – Flowchart of the FinnBladder-6 study.
A1 = bacillus Calmette-Guérin 12 mo; A2 = bacillus Calmette-Guérin 24 mo; B1 = epirubicin and interferon 12 mo; B2 = epirubicin and interferon 24 mo; BCG = bacillus Calmette-Guérin; C = cystoscopy and cytology every 3 mo; IFN = interferon; R = randomization; TURB = transurethral resection of the bladder; ↑↓ = bladder instillation therapy.

Table 1 – Patient characteristics

	BCG (%)	EPI/IFN (%)	*p* value
No. of eligible patients	115	114	0.5[a]
No. of patients in 1-yr maintenance group	64 (56)	59 (52)	0.6[a]
No. of patients in 2-yr maintenance group	51 (44)	55 (48)	
Male	85 (74)	84 (74)	1[a]
Female	30 (26)	30 (26)	
Age, mean/median, yr	68/71	67/70	0.9[b]/0.7[c]
First/third quartile [range]	62/77 [32–89]	60/77 [32–87]	
Prior recurrence rate, no. of recurrences/year			
Mean/median	1.8/1.5	1.9/1.6	0.2[b]/0.7[c]
First/third quartile	1.0/2.4	1.0/2.5	
Time to prior recurrence, d			
Mean/median	181/133	211/138	0.9[c]/0.9[c]
First/third quartile	105/201	107/215	
Tumors at randomization, solitary/multiple/missing	34/76/5 (30/66/4)	28/84/2 (25/74/2)	0.3[a]
Tumor size, cm			0.6[a]
<1	79 (69)	77 (68)	
1–3	15 (13)	19 (17)	
>3	0 (0)	1 (1)	
Missing	21 (18)	17 (15)	
T category			0.2[a]
pTa/pT1/urothelial neoplasm	103/10/2 (90/9/2)	108/6/0 (95/5/0)	
Grade			0.8[a]
1	75 (65)	79 (69)	
2	27 (24)	24 (21)	
Low malignant potential	6 (5)	3 (3)	
Low grade	5 (4)	5 (4)	
Other/missing	2 (2)	3 (3)	
Cytology, positive[*]/negative/missing	5/53 /57 (4/46/50)	10/60/44 (9/53/39)	0.2[a]
Perioperative instillation given			
Yes/no/missing	93/20/2 (81/17/2)	93/23/1 (79/20/1)	0.3[a]
Prior instillation therapy, yes/no/missing	7/99/9 (6/86/8)	3/105/6 (3/92/5)	0.3[a]

BCG = bacillus Calmette-Guérin; EPI = epirubicin; INF = interferon-α2a.
[*] Papanicolaou class 4–5.
[a] Chi-square test.
[b] Unpaired *t* test.
[c] Mann-Whitney test.

and EPI/IFN groups. The median overall follow-up time based on survival data was 7.5 yr (maximum: 14.0) and 7.4 yr (maximum: 13.7), respectively. The median follow-up time of those alive at the latest check-up was 8.1 and 8.0 yr in the BCG and the EPI/IFN group, respectively.

The probability of recurrence was significantly lower in the BCG group than in the EPI/IFN group (hazard ratio [HR]: 0.41; 95% confidence interval [CI], 0.28–0.60; $p < 0.001$) (Fig. 2). At 7.4 yr, the probability of recurrence was 39% versus 72% in the BCG vs EPI/IFN group, respectively.

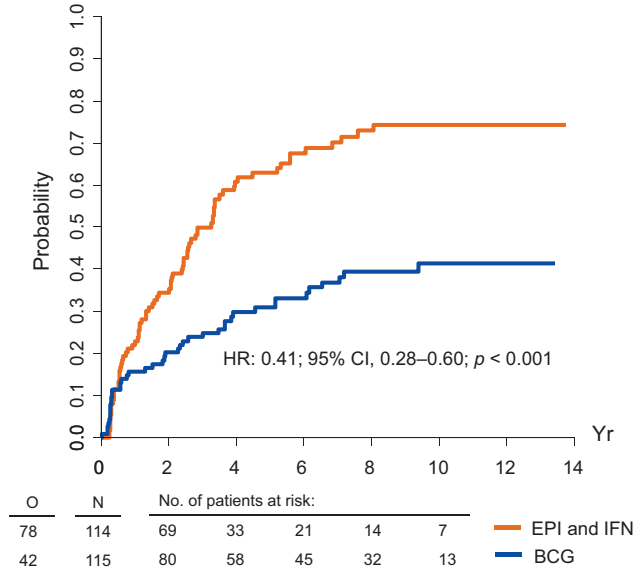


Fig. 2 – The cumulative incidence curves of time to first recurrence in the pooled 1- and 2-yr maintenance bacillus Calmette-Guérin group and in the pooled 1- and 2-yr maintenance epirubicin plus interferon group.
BCG = bacillus Calmette-Guérin; CI = confidence interval; EPI = epirubicin; HR = hazard ratio; IFN = interferon; N = number of patients; O = observed number of events.

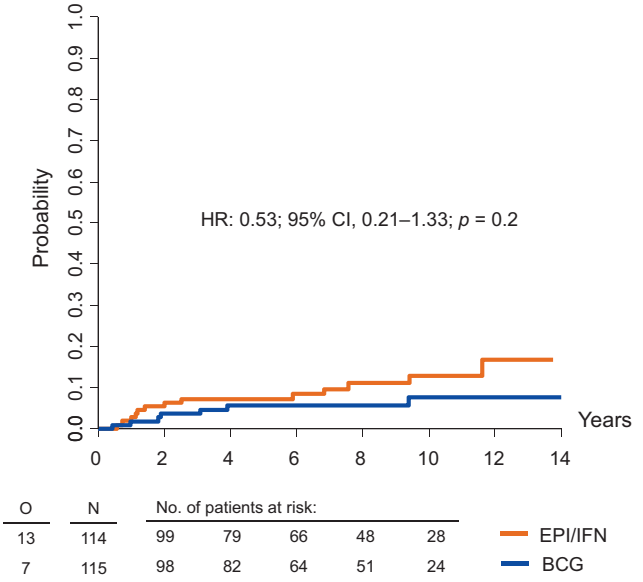


Fig. 3 – The cumulative incidence curves of time to progression in the pooled 1- and 2-yr maintenance bacillus Calmette-Guérin group and in the pooled 1- and 2-yr maintenance epirubicin plus interferon group.
BCG = bacillus Calmette-Guérin; CI = confidence interval; EPI = epirubicin; HR = hazard ratio; IFN = interferon; N = number of patients; O = observed number of events.

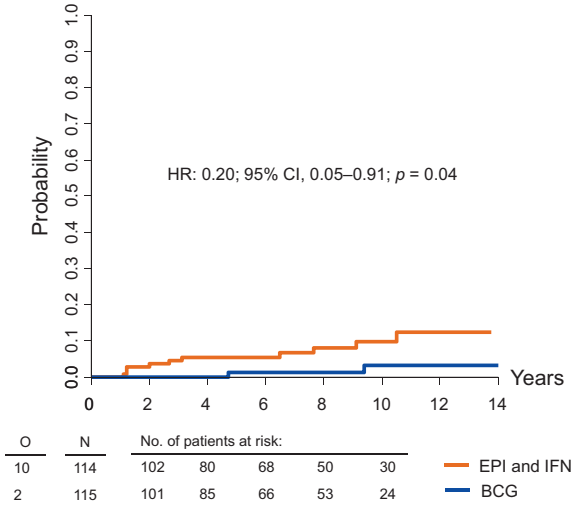
The number of patients with progression was low, and there was no significant difference between the BCG and EPI/IFN groups (Fig. 3). However, there was a significant difference in DS mortality in favor of the BCG group (HR: 0.20; 95% CI, 0.05–0.91; $p = 0.04$) because 10 of 13 patients with progression in the EPI/IFN group died of BCa compared with 2 of 7 in the BCG group. The relative risk of dying from BCa was reduced 80% in the BCG group (Fig. 4).

There was no significant difference in the OS between the groups (Fig. 4).

Table 1 reports the number of patients who did not receive a single perioperative instillation of EPI, and Supplementary Table 1 shows the number of other missing instillations and reasons for treatment cessation in each arm.

Twenty-nine patients in the EPI/IFN groups were treated with additional instillation therapies compared with only seven in the BCG group (Supplementary Table 2). Seven cystectomies and five radiotherapies were recorded in the EPI/IFN group compared with four and two in the BCG group, respectively.

Table 2 summarizes the results of the univariable analysis of potential predictors for the primary and the secondary end points. All significant predictors of the univariable analyses



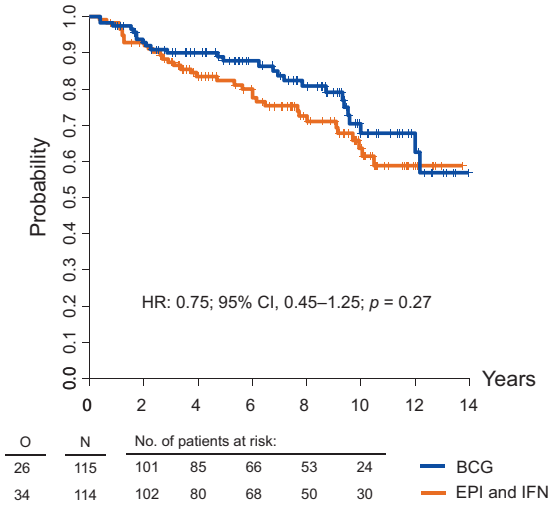


Fig. 4 – The cumulative incidence curves of disease-specific mortality and the Kaplan-Meier curves of overall survival in the pooled 1- and 2-yr maintenance bacillus Calmette-Guérin group and in the pooled 1- and 2-yr maintenance epirubicin plus interferon group.
BCG = bacillus Calmette-Guérin; CI = confidence interval; EPI = epirubicin; HR = hazard ratio; IFN = interferon; N = number of patients; O = observed number of events.

Table 2 – Univariable analysis of baseline variables for primary and secondary end points

	Primary end point				Secondary end points [##]							
	First recurrence				Progression				Bladder cancer mortality			
Variable	HR	95% CI	1 / HR	*p* value	HR	95% CI	1 / HR	*p* value	HR	95% CI	1 / HR	*p* value
Gender, men vs women	0.98	0.66–1.45	1.02	0.9	1.45	0.58–3.63	0.69	0.4	1.30	0.40–4.23	0.77	0.7
Age, yr	1	0.99–1.02	1	0.7	1.02	1.02–1.10	0.95	0.001	1.08	1.04–1.12	0.93	<0.001
Median, <70.6 vs ≥70.6	1.07	0.75–1.53	0.93	0.7	3.39	1.24–9.31	0.30	0.02	5.71	1.29–25.2	0.18	0.02
Mean, <67.8 vs ≥67.8	0.97	0.68–1.39	1.03	0.9	3.17	1.06–9.5	0.31	0.04	8.85	1.17–67.0	0.11	0.04
Recurrence rate, no. of recurrences per year	1.03	0.87–1.22	0.97	0.7	0.80	0.53–1.24	1.24	0.3	0.79	0.44–1.42	1.27	0.4
Time to preceding recurrence, d	1	0.98–1.00	1	0.2	1	0.99–1.00	1	0.4	0.99	0.99–1.00	1.01	0.02
Third quartile, ≥210 vs <210 d	1.62	1.02–2.55	0.62	0.04	1.88	0.55–6.48	0.53	0.4	4.69	0.62–35.6	0.21	0.1
Multiple vs solitary tumors	0.91	0.61–1.35	1.03	0.6	1.58	0.63–3.99	0.63	0.3	0.94	0.26–3.25	1.07	0.9
T1 vs Ta	0.94	0.48–1.86	1.06	0.9	0.16	0.06–0.41	6.35	<0.001	0.14	0.04–0.44	7.31	<0.001
Grade, <2 vs 2	0.93	0.59–1.48	1.07	0.76	1.85	0.73–4.69	0.54	0.2	2.20	0.72–6.72	0.45	0.2
Cytology, positive vs negative/ missing	0.45	0.24–0.86	2.21	0.02	0.15	0.06–0.40	6.72	<0.001	0.07	0.02–0.21	14.7	<0.001
Cytology, positive vs negative	0.39	0.20–0.79	2.54	0.009	0.09	0.03–0.31	10.6	<0.001	0.08	0.02–0.28	12.3	<0.001
Tumor diameter, ≥1 vs <1 cm	0.84	0.49–1.42	1.20	0.5	0.71	0.20–2.56	1.41	0.6	0.31	0.07–1.33	3.28	0.1
Perioperative epirubicin, no vs yes	0.66	0.44–0.98	1.52	0.04	0.65	0.24–1.74	1.55	0.4	1.03	0.22–4.77	0.97	1

CI = confidence interval; HR = hazard ratio.
[##] Cytology was additionally a significant predictor of the other secondary end point, overall survival (HR: 0.39; 95% CI, 0.19–0.79; $p = 0.009$ for positive vs negative/missing cytology; HR: 0.33; 95% CI, 0.16–0.72; $p = 0.005$ for positive vs negative cytology).

remained significant and retained the magnitude of their HR in the multivariate analysis when adjusted together with the treatment group. Positive cytology was a significant predictor for all end points.

4. Discussion

In the present study on patients belonging to the intermediate- and high-risk groups of NMIBC without CIS, BCG treatment was far more effective in preventing recurrence than EPI/IFN. We additionally observed significantly fewer BCa deaths in the BCG group than in the EPI/IFN group.

At the time of our study design, some promising preliminary results of IFN-α therapy were observed. Portillo Martin et al [13] compared instillations of IFN-α 60 mU with the control group with no instillations in patients with T1 G2–3 or recurrent G1 tumors. After the follow-up of 22.4 mo, they found a reduction in recurrence of 40% versus 46.6% and, more importantly, a difference in grade and/or stage progression of 8.3% versus 35.7% in the IFN-α instillation group versus the control group, respectively. A Finnish study [12] compared TURB alone with regimens involving epirubicin 50 mg or a combination of epirubicin 50 mg plus IFN-α2b 10 mU. EPI monotherapy and the combination therapy significantly reduced recurrence compared with TURB alone, and in addition, there was a nonsignificant difference in favor of the combination therapy over EPI monotherapy.

In a Nordic study of 250 eligible patients with primary T1 G2–3 tumors with or without CIS, patients were treated with a 2-yr SWOG BCG regimen or EPI/IFN regimen identical to ours apart from the perioperative EPI [14,15]. After 5 yr, the recurrence-free estimate of the BCG group was significantly better than that of the EPI/IFN group, 59% versus 38%, respectively [14]. Based on a subgroup analysis, the difference was highly significant only among patients with concomitant CIS. In our study, we found a significant difference between the study groups involving patients with recurrent and mainly Ta disease but no CIS. The risk of recurrence in patients with T1 disease without CIS in the EPI/IFN group of the Scandinavian study was lower than the risk in the patients in our EPI/IFN group. The re-resection applied in the study by Hemdan et al study obviously decreased the number of potential recurrences [15].

Assuming that the impact of IFN on the outcome of our EPI/IFN group was minimal, the best match for our study is the European Organization for Research and Treatment of Cancer (EORTC) trial 30911 [16]. The trial involved 957 intermediate- and high-risk BCa patients who were treated with six weekly instillations followed by the 3-yr SWOG maintenance schedule using EPI, BCG, or BCG plus isoniazid. After a median follow-up of 9.2 yr, the BCG regimens were significantly better than the EPI regimen. Incidentally, the estimates for the risk of recurrence of the pooled BCG groups in the EORTC and those in our study were identical while the corresponding estimates of the EORTC EPI group was >10% better than that of our EPI/IFN group. The smaller difference between the BCG and EPI groups in the EORTC trial may reflect a lower risk of recurrence than in our study. As many as 45% of the patients in the EORTC study presented with primary tumors, whereas all the patients in our study had recurrent tumors.

In addition to EORTC trial 30911, two other recent studies [17,18] involved BCG arms and applied the cumulative incidence analysis. In the study by Solsona et al, BCG maintenance comprised only three instillations administered 2 wk apart; in the study by Oddens et al, the 1- or 3-yr SWOG schedule was used. As many as 58.5%

versus 68.1% of patients had primary tumors and 13.2% versus 44% had solitary tumors in the two studies, respectively, whereas all the patients in our study had recurrent tumors with 72% of them multiple.

Detailed comparisons between separate studies should be made with caution. However, the recurrence estimates for the BCG arms in the two studies and in EORTC trial 30911 are similar, with the risk of recurrence in these studies at best approximately 35% at 6 yr and 40% at 10 yr. Although our patients possibly had the highest risk of recurrence, the outcome in our BCG arm was as good as that in the three studies.

The excellent efficacy of the monthly maintenance instillations is in disagreement with the impression given in the original SWOG report [2]. The SWOG study was merely designed to compare BCG maintenance with no maintenance and excluded patients with recurrence before maintenance therapy. Therefore, all eligible patients were disease free at 3 mo. The authors compared the disease-free plots of their subgroup of patients with NMIBC without CIS with those of their two other studies [5,19] without similar exclusion. This resulted in an artificial difference of approximately 20–25% at 3 mo in favor of the SWOG maintenance over the two studies with monthly BCG maintenance [2]. There have been controversial results of the efficacy of maintenance therapy with BCG versus no maintenance at all [20,21]. Badalament et al and Akaza et al each published NMIBC studies with relatively good results without any BCG maintenance protocol. The former involved a relatively small number of patients and a short follow-up. The study design of Akaza et al was very different from ours, with no initial TURB performed at the first phase of the study. At 3 yr, the tumor nonrecurrence rates were 74% versus 77% in the 8-wk induction only versus the 12-mo maintenance groups, respectively. Direct comparisons with our study seem problematic with such a different trial setting.

The inclusion criteria of the present study were identical to those of two of our earlier studies, FinnBladder-1 and FinnBladder-4 [4,22]. Interestingly, the outcome of the BCG arm of the recently published long-term results of the FinnBladder-4 study was similar to that of the present study, even though the induction period in the FinnBladder-4 study comprised MMC instillations instead of BCG. The risk of recurrence was approximately 10% higher in the FinnBladder-1 study. One explanation is that no perioperative chemotherapy was used in the FinnBladder-1 study unlike in the two newer studies. Based on the analysis of the proportional subdistribution hazards model, the patients in the present study who failed to get the perioperative instillation were more likely to have a further recurrence, which is consistent with our earlier results from the FinnBladder-4 study [4] (Supplementary Fig. 3).

The risk of progression or DS mortality in the present study was low. Most of the patients with progression in the EPI/IFN group died of BCa, resulting in a significant difference in DS mortality between the two groups. The high risk of dying of BCa in case of progression reflects the fact that the meticulous and expensive follow-up aimed at detecting progression early enough to prevent deaths was not effective in patients treated with EPI/IFN instillations.

One of the weaknesses of the present study was the markedly prolonged enrollment time, causing a great variation in the individual follow-up times. We also had relatively many randomization failures and some missing data. These limitations do not impair our main finding, the highly significant difference in recurrence between the two treatment groups. In contrast, the low number of end-point events other than recurrence is still another weakness of our study. Reflecting on the insufficient power of the present study regarding the other end points, just a few more events in either treatment group would have turned the *p* value significant or nonsignificant considering progression and DS mortality.

Positive cytology was a significant predictor for all of our end points. According to our limited data, it seems unwise to select EPI-based instillation therapy in case of intermediate-risk patients with positive cytology.

5. Conclusions

One perioperative chemotherapy instillation followed by induction and monthly maintenance therapy for at least 1 yr with BCG reduced the risk of recurrence compared with combined instillation therapy of EPI and IFN in frequently recurrent BCa patients. Although lacking prospective comparisons, the BCG regimen involving monthly BCG maintenance instillations appears to have an efficacy very similar to that of several recent large trials conducted with cumulative incidence analysis.

The abstract of the study was published in the Proceedings of the Annual European Association of Urology Congress; March 11–15, 2016; Munich, Germany.

Author contributions: Timo Marttila 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: Marttila, Kaasinen, Raitanen.
Acquisition of data: Marttila, Järvinen, Liukkonen, Rintala, Boström, Seppänen, Tammela, Hellström, Aaltomaa, Leskinen, Raitanen, Kaasinen.
Analysis and interpretation of data: Kaasinen, Marttila, Järvinen, Liukkonen.
Drafting of the manuscript: Kaasinen, Marttila, Järvinen, Liukkonen.
Critical revision of the manuscript for important intellectual content: Kaasinen, Marttila, Järvinen, Liukkonen.
Statistical analysis: Kaasinen.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Kaasinen, Liukkonen.
Other (specify): None.

Financial disclosures: Timo Marttila certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

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.2016.03.034.

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