Adjuvant chemotherapy for superficial transitional cell bladder carcinoma: long-term results of a European organization for research and treatment of cancer randomized trial comparing doxorubicin, ethoglucid and transurethral resection alone

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ADJUVANT CHEMOTHERAPY FOR SUPERFICIAL TRANSITIONAL CELL BLADDER CARCINOMA: LONG-TERM RESULTS OF A EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER RANDOMIZED TRIAL COMPARING DOXORUBICIN, ETHOGLUCID AND TRANSURETHRAL RESECTION ALONE

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ABSTRACT

Purpose: We compared the efficacy of transurethral resection alone or transurethral resection followed by bladder instillations of doxorubicin or ethoglucid for 1 year in patients with superficial bladder carcinoma, and followed them long term for the incidence of progression to muscle invasion.

Materials and Methods: A total of 443 patients with superficial transitional cell carcinoma of the bladder was randomized. After randomization of 206 patients the control arm was closed to patient entry based on the results of an interim analysis showing a significant difference in favor of those receiving adjuvant chemotherapy.

Results: Final analysis of treatment results for recurrence included 432 patients at a median followup of 3.4 years for time to first recurrence, 5 years for analysis of time to invasion (Category T2 disease or worse) and 10.7 years for duration of survival. Time to first recurrence was significantly prolonged by both drugs compared to transurethral resection alone (doxorubicin versus transurethral resection alone $p < 0.001$ and ethoglucid versus control $p < 0.001$). Recurrence rate per year was 0.30 for both adjuvant treatment arms and 0.68 for the resection only group. Progression to muscle invasion was rare (15.1% of cases) and not apparently different in the 3 treatment arms. Of the 423 patients death from any cause in 199 and from malignant disease in 59 was not correlated with treatment. However, there was a strong correlation between death from malignant disease, and T category and tumor grade.

Conclusions: In regard to time to first recurrence and recurrence rate per year this study indicates that adjuvant chemotherapy with doxorubicin and ethoglucid using the indicated schedule is superior to transurethral resection alone. However, progression in stage or survival was not influenced by the treatment regimen.

KEY WORDS: bladder; bladder neoplasms; carcinoma, transitional cell; doxorubicin; drug therapy

How far patients with Ta/T1 bladder tumors may benefit from adjuvant intravesical chemotherapy remains an open question, specifically when considering not only prevention of recurrence but also the more important prevention of progression. In the present study patients were treated with transurethral resection followed by adjuvant chemotherapy with doxorubicin or ethoglucid, or by transurethral resection alone. In 1984 the preliminary results of this trial were published.[1] We reported that the control arm was closed to patient entry based on the results of an interim analysis showing a recurrence rate of 1.1 per year in the transurethral resection only group compared to 0.34 in both adjuvant treated groups. This difference was highly significant ($p < 0.001$). We now report long-term results with emphasis on time to invasion, duration of survival and death from malignant disease.

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METHODS

Objectives of the study. The objectives of the study were to compare time to first recurrence, recurrence rate and incidence of progression to muscle invasion after transurethral resection alone, transurethral resection followed by intravesical doxorubicin or transurethral resection followed by intravesical ethoglucid chemotherapy.

TABLE 1. *Patient population, including 443 randomized at 21 institutions*

	No. Pts.
Randomized	443
Ineligible	18
Eligible	425
Without followup	2
Included in analysis	423

TABLE 2. *Distribution according to treatment arm*

	No. Pts. Randomized	No. Pts. Eligible
Doxorubicin	191	182
Ethoglucid	179	171
Control	73	72
Totals	443	425

TABLE 3. *Median duration of followup*

	Median Yrs. Followup
Time to:	
First recurrence	3.4
Invasion	5.0
Distant metastases	6.4
Death due to malignant disease	7.2
Duration of survival	10.7

TABLE 4. *Patient characteristics according to treatment group*

	No. Pts. (%)		
	Doxorubicin (182 pts.)	Ethoglucid (171 pts.)	Control (72 pts.)
T category:			
T0	0	1 (1)	0
Tis	7 (4)	4 (3)	1 (1)
Ta	91 (50)	87 (51)	42 (58)
T1	82 (45)	77 (45)	29 (40)
Unknown	1 (1)	1 (1)	0
Grade:			
0	15 (8)	16 (9)	11 (15)
1	78 (43)	73 (43)	29 (40)
2	59 (33)	61 (36)	26 (36)
3	22 (12.2)	2 (1)	1 (1)
Unknown	7 (4)	7 (5)	4 (5)
Tumor size (cm.):			
Less than 1	65 (36)	52 (31)	28 (39)
1–3	85 (47)	93 (55)	34 (47)
More than 3	29 (16)	24 (14)	10 (14)
Unknown	2 (1)	1 (1)	0
No. tumors:			
1	79 (44)	73 (43)	31 (43)
2–3	58 (32)	57 (34)	28 (39)
More than 3	43 (24)	39 (23)	13 (18)
Unknown	1 (1)	1 (1)	0
Prior recurrence rate:			
Primary	125 (69)	117 (68)	47 (65)
Less than 1/yr.	21 (12)	31 (18)	6 (8)
1/Yr. or greater	34 (19)	21 (12)	19 (26)
Unknown	1 (1)	1 (1)	0
Sex:			
M	145 (80)	143 (84)	65 (90)
F	35 (19)	26 (15)	7 (10)
Unknown	1 (1)	1 (1)	0
Age (yrs.):			
Younger than 50	14 (8)	14 (8)	5 (7)
50–59	38 (21)	32 (19)	20 (28)
60–69	51 (28)	60 (35)	25 (35)
70–79	70 (39)	51 (30)	17 (24)
80 or Older	7 (4)	12 (7)	5 (7)
Unknown	1 (1)	1 (1)	0
Days from transurethral resection to instillation:			
0–3	19 (11)	13 (8)	
4–14	129 (71)	130 (77)	
Greater than 14	25 (14)	22 (13)	
Unknown	8 (4)	5 (3)	

Selection of patients. All patients with histologically proved, transurethrally resectable primary or recurrent category Ta and T1 transitional cell carcinoma of the bladder or carcinoma in situ were considered eligible for the trial. Tumors were classified according to the 1978 TNM classification of the International Union Against Cancer. All visible lesions were completely resected. Pathologically no tumor infiltrated beyond the lamina propria.

Design of the trial. Within 1 week of transurethral resection certain treatments were randomly allocated, including intravesical doxorubicin, intravesical ethoglucid and no other treatment. Doxorubicin and ethoglucid were administered weekly for 1 month and then monthly thereafter for a total of 11 months. Recurrent tumors, if observed 1 year or less after randomization, were resected and weekly intravesical treatment was initiated. However, total duration of intravesical treatment was limited to 1 year after the first transurethral resection. Patients were followed until the first recurrence was detected after completion of 1 year of treatment in the adjuvant treated groups or until the first recurrence after 1 year of followup in the transurethral resection only group. Further treatment was at the discretion of the local investigator. All patients continued to be monitored for time to invasion and survival.

Therapeutic regimens. Doxorubicin (50 mg. diluted in 50 ml. normal saline) or ethoglucid (1.13 gm. diluted in 100 ml. sterile water) was instilled into the bladder 3 to 14 days after transurethral resection and retained for 1 hour. Nitrofurantoin (100 mg.) was given after each instillation 3 times daily for 3 days. White blood and platelet counts, and urinalysis were obtained before each chemotherapy administration. Chemotherapy was delayed until the white blood count was 4×10^9/l. or greater and the platelet count was 1.5×10^9/l. or greater. Chemotherapy was also delayed whenever bacterial cystitis was present until the infection was controlled. If drug induced cystitis recurred repeatedly, the drug was given in a solution of twice the usual volume.

Evaluation of therapy. Cystoscopy was repeated every 12 weeks during year 1, every 16 weeks during year 2 and every 24 weeks thereafter in patients without recurrence. All lesions visible on cystoscopy were biopsied with recurrence established only by histological examination of the biopsy material. If cytology was positive and no lesion was visible on cystoscopy, random biopsies were done. All participants were asked to send representative unstained histological slides from all resected material for central pathology review.

Criteria of evaluation. Time to first recurrence was defined as the time from randomization until the first cystoscopy at which recurrence was observed. Recurrence rate per year was defined relative only to cystoscopy performed before the patient was removed from the study, using the formula, number of positive cystoscopies/the period (expressed in years) between randomization and the last cystoscopy performed while the patient remained in the study. Increase in T category was defined as progression to stage T2 disease or worse. Patients without progression were censored at the last followup cystoscopy. Survival was defined from the date of randomization until death. Patients still alive or lost to followup were censored at the last date they were known to be alive. Median duration of followup for an event is the duration of followup, such that half of the patients had been followed for a period shorter than the median and half had been followed for a period longer than the median.

Statistical methods. Time to event curves (first recurrence and survival) were estimated using the Kaplan-Meier technique[2] and compared using the log rank test.[3] For ordered categories with more than 2 levels a log rank test for trend was used. Differences in recurrence rates were tested using a nonparametric permutation test.

RESULTS

Between December 1979 and December 1983, 443 patients were randomized by institution to doxorubicin, ethoglucid or transurethral resection alone. Because the control arm

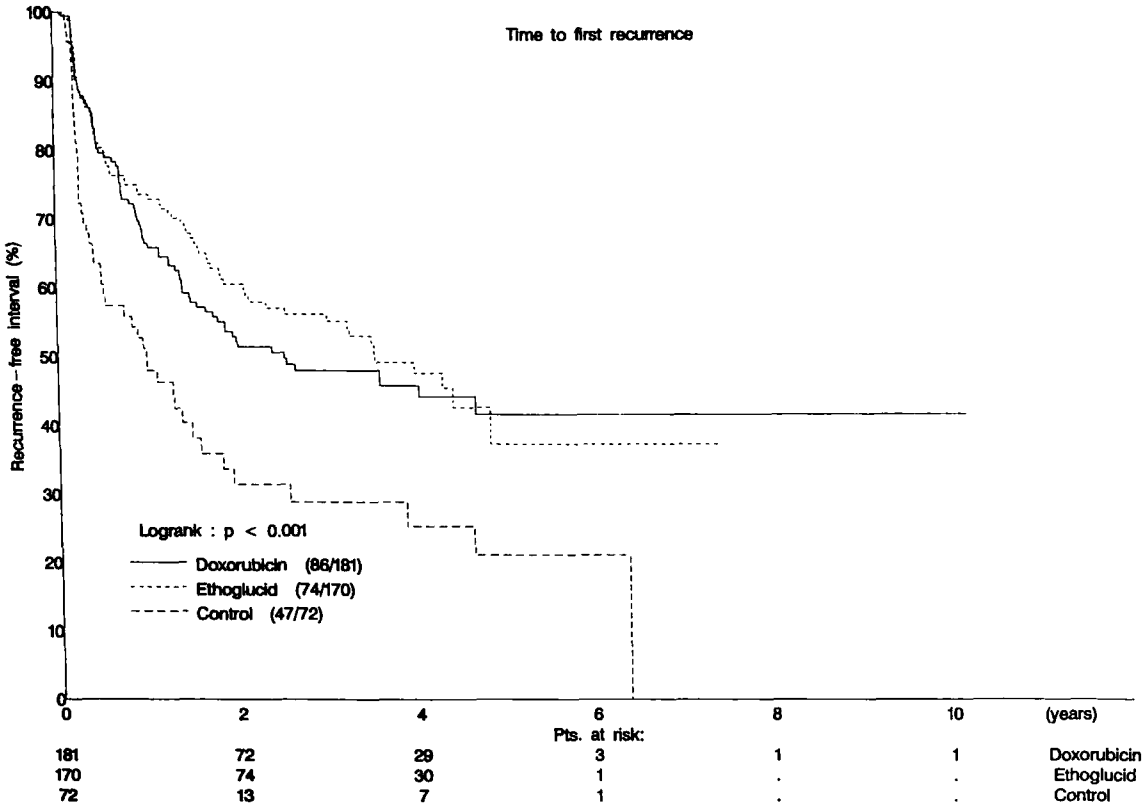


FIG. 1. Time to first recurrence in all patients according to treatment group

TABLE 5. *Recurrence at first followup cystoscopy*

Treatment Arm	No. Any Site (%)	No. Same Site	No. Without Recurrence (%)
Doxorubicin	23 (13.8)	9	143 (86.2)
Ethoglucid	23 (14.7)	15	133 (85.3)
Control	23 (32.8)	12	47 (67.2)
Totals	69 (17.6)	36	323 (82.4)

TABLE 6. *Recurrence rate per year according to treatment group*

	Doxorubicin	Ethoglucid	Control
No. pts. evaluated	166	156	70
No. pts. with recurrence (%)	83 (50)	73 (47)	47 (67)
Total No. recurrences	118	106	85
Recurrence rate/yr.	0.30	0.30	0.68

For doxorubicin versus control and ethoglucid versus control $p < 0.0001$, not significant for doxorubicin versus ethoglucid.

(transurethral resection only) was closed to patient entry based on interim analysis after 206 patients had been entered,[1] fewer patients were randomized to the control group. A total of 425 patients was eligible for study with followup data available on recurrence for 392 and survival for 423 (tables 1 to 3). Table 4 shows the distribution of eligible patients by treatment group, initial T category, grade of malignancy, number of tumors present, size of tumors, previous treatment, and stratification for primary and recurrent tumors. In all treatment arms 68% of the cases were newly diagnosed at the time of trial entry and the others were recurrent Ta or T1 tumors. Median followup was 3.4 years for recurrence, 5 for invasion, 7.2 for time to death from malignant disease and 10.7 (maximum followup 14) for duration of survival.

Time to first recurrence. Kaplan-Meier curves are shown by treatment group for all eligible patients with followup. A global comparison by treatment was highly significant ($p < 0.001$, fig. 1). Paired comparisons yielded a significant difference between doxorubicin and the control group ($p < 0.001$) and ethoglucid and the control group ($p < 0.001$) in favor of adjuvant chemotherapy. A comparison of doxorubicin with ethoglucid yielded no significant difference ($p = 0.48$). These results were similar when analyzed separately for newly diagnosed (global comparison $p = 0.03$) and recurrent tumors (global comparison $p = 0.002$). The benefit of adjuvant chemotherapy was also noted for Ta (global comparison $p = 0.05$) and T1 (global comparison $p < 0.001$) tumors. Thus, adjuvant chemotherapy significantly prolonged the time to first recurrence. At 3 years 48% of the patients on doxorubicin (95% confidence interval 40 to 56) and 56% on ethoglucid (95% confidence interval 48 to 64) were recurrence-free. In the control group 29% of the patients had not had recurrence

TABLE 7. *Increase in T category*

Treatment	No. Pts.	No. During Treatment (%)	No. After Treatment (%)	No. Any Time (%)
Doxorubicin	181	12 (6.6)	13 (7.2)	25 (13.8)
Ethoglucid	170	15 (8.8)	11 (6.5)	26 (15.3)
Control	72	5 (6.9)	8 (11.1)	13 (18.1)
Totals	423	32 (7.6)	32 (7.6)	64 (15.1)

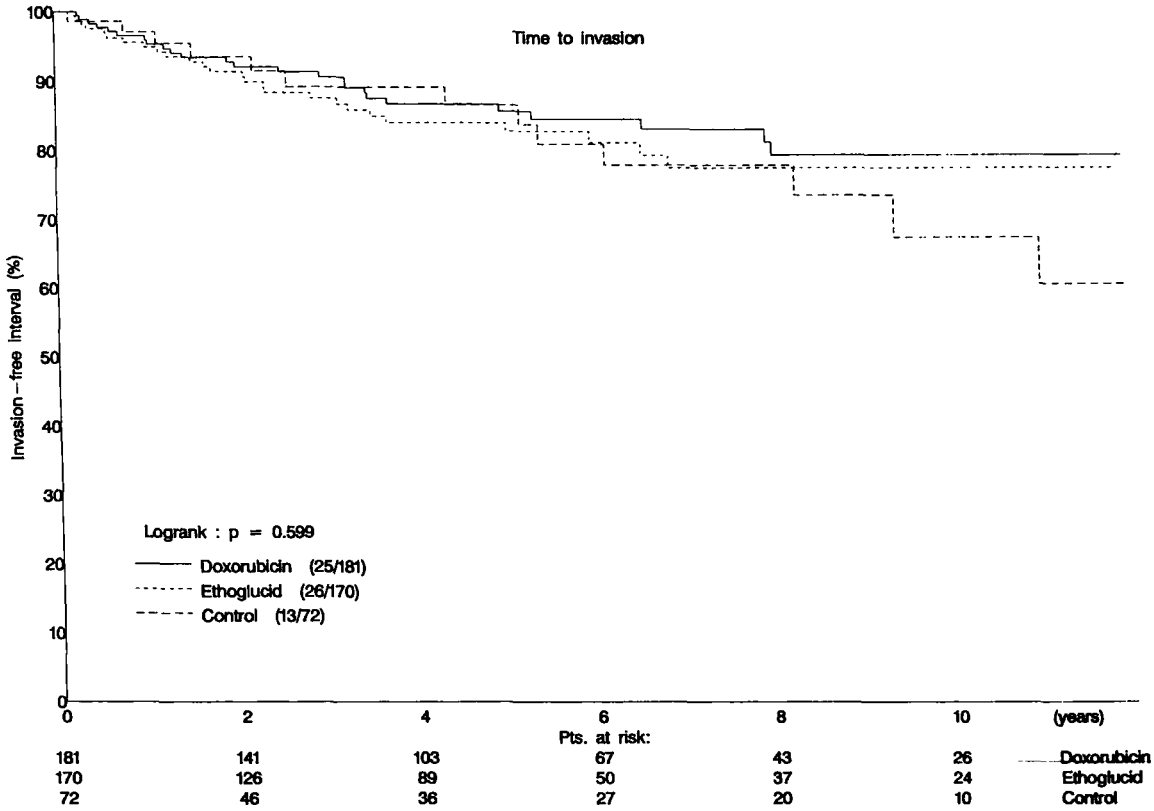


FIG. 2. Time to invasion according to treatment group

at 3 years (95% confidence interval 17 to 41). Of the 392 patients analyzed 69 (16.3%) already had recurrence at the first followup cystoscopy, including 36 (52%) who had a tumor at the same site as at trial entry (table 5).

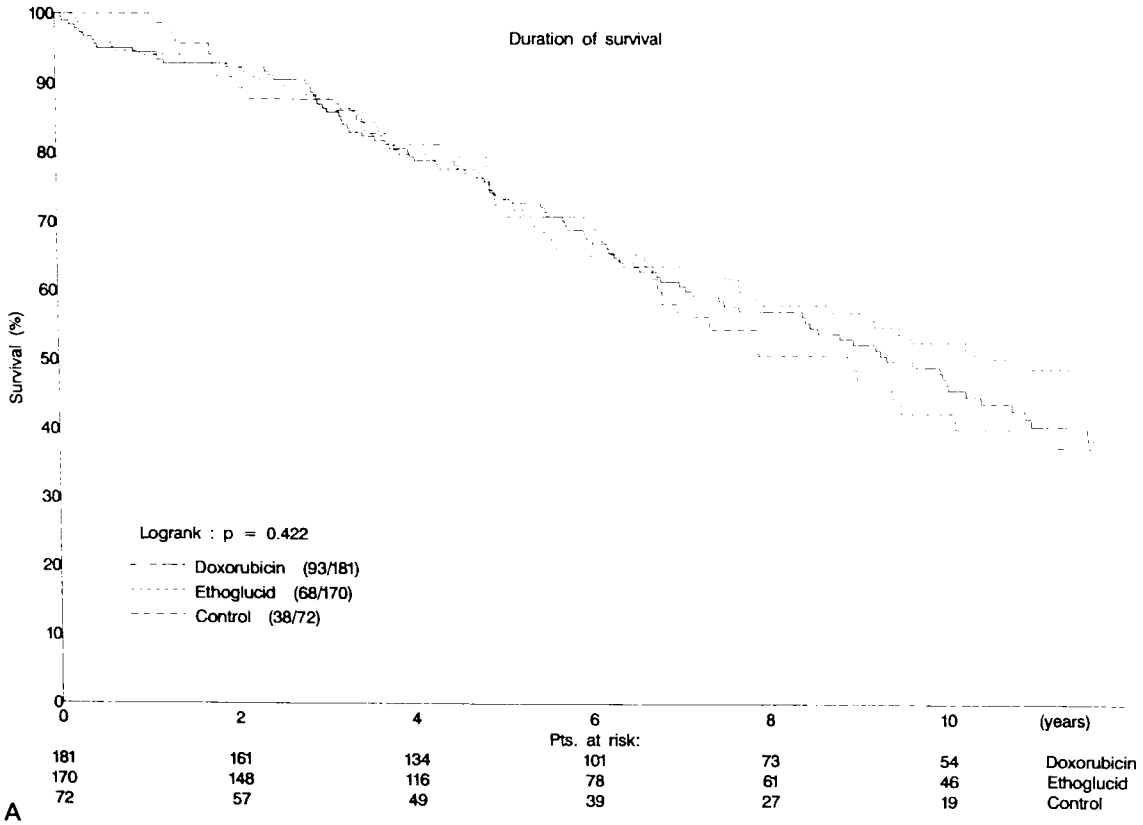
Recurrence rate per year. Table 6 shows the recurrence rate per year according to treatment. Comparisons were performed globally for all patients, and separately for those with primary and recurrent tumors. No difference was detected between the doxorubicin and ethoglucid groups but each drug decreased the recurrence rate significantly compared to the control group. Similar results were obtained for patients with primary ($p = 0.04$ for doxorubicin versus controls and $p = 0.001$ for ethoglucid versus controls) and recurrent ($p < 0.001$ for doxorubicin versus controls and $p = 0.001$ for ethoglucid versus controls) tumors.

Increase in T category and distant metastases. A total of 64 patients reported an increase in T category to T2 or worse, including 32 in the first year after randomization (27 , 7.7%, received intravesical treatment and 5, 6.9%, were controls) and 32 were noted during followup for recurrence and/or progression (table 7). Of the 221 cases categorized as Ta 20 (9%) and of the 188 with a T1 tumor 42 (22.3%) progressed to T2 disease or worse. No association between treatment and an increase in T category was noted (fig. 2). Distant metastases developed in 20 patients, including 16 who also had an increase in T category to T2 or worse.

Survival. Of the 423 eligible patients with followup 119 died (47%), including 59 (14%) of malignant disease, of whom 31 had an increase in T category to T2 or worse. There was no significant difference in overall survival according to treatment group ($p = 0.422$) (fig. 3). In 10 patients (2.4%) transitional cell carcinoma of the upper urinary tract developed and 5 died. Of the 57 patients who had a second primary tumor 41 died during followup. Thus, death from malignant disease must be interpreted as death from bladder tumor or a second primary tumor. The second primary cancers were in the prostate in 18 patients, lung in 13, colon/rectum in 4, skin in 4, and kidney, breast, esophagus, pancreas, larynx, oral cavity and choledochus in 13. One patient had a melanoma, 1 had a histiocytoma and 3 had an unspecified second primary tumor. Survival, defined as time to death from malignant disease, was related to T category ($p = 0.04$ for Ta versus T1), prior recurrence rate ($p = 0.02$ for primary, or 1 or less recurrence per year versus greater than 1) and grade ($p = 0.006$, table 8). Table 9 shows treatment comparisons for these end points.

Pathological review. Pathology reports were available for 318 patients. Of 131 stage pT1 tumors 66 (50.3%) were changed to stage pTa after pathology review. Thus, the review pathologist tended to report a lesser degree of tumor infiltration than the local pathologist. On the other hand, the review pathologist tended to increase the degree of malignancy. Of the 135 patients with grade 1 disease 64 (47%) and of the 113 with grade 2 disease 26 (23%) had the degree of malignancy increased by the review pathologist. Overall local and review pathologists agreed in 84.5% of cases for stage Ta, 44.3% for T1 disease and 52.3% for grade. Furthermore, muscle invasive tumors (all stage T2) in 4 of 318 patients were missed by the local pathologist. When the T category and grade of malignancy were based on review pathology, their prognostic importance became more pronounced than when based on local stage and grade (table 8).

Toxicity. Data on toxicity were available for 342 patients (table 10). The main toxicity was bacterial and chemical cystitis of which the latter caused 4 patients to stop the instillations, including 2 after doxorubicin and 2 after ethoglucid. Systemic side effects, such as allergic reaction, mild nausea, diarrhea and vomiting, developed in 9 of 176 pa-



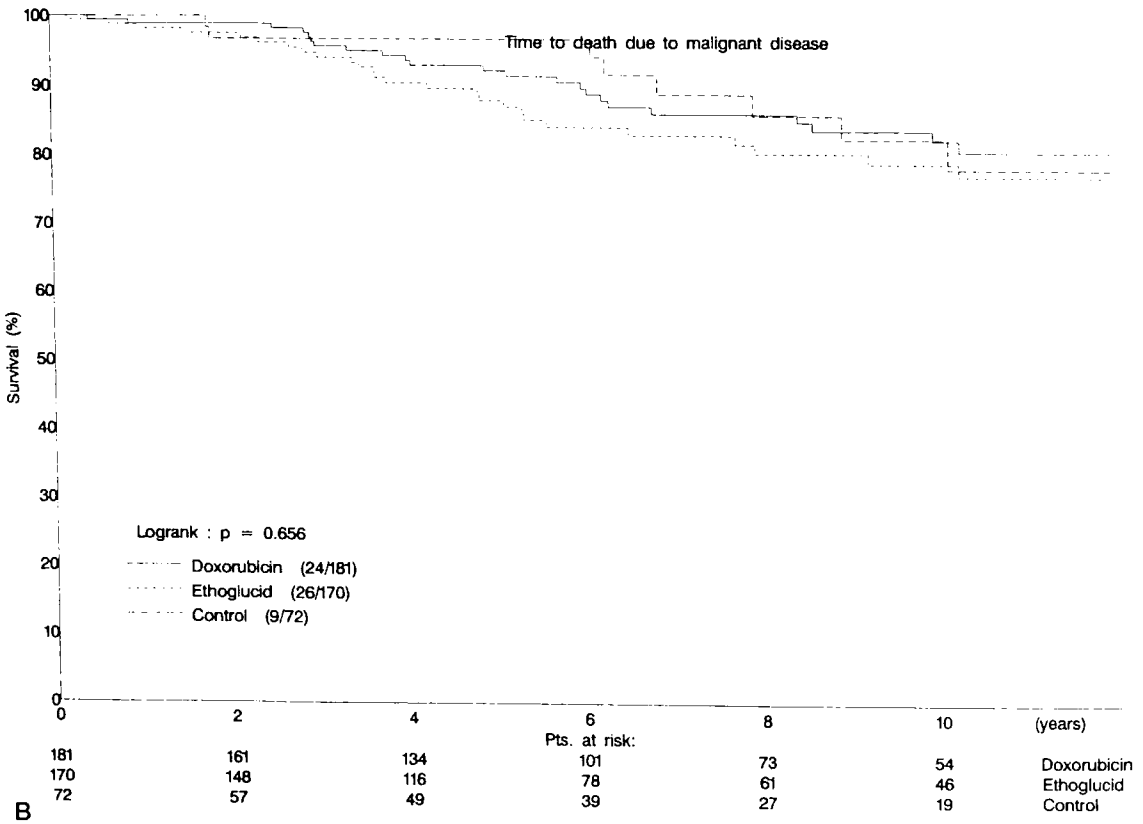


FIG. 3. Treatment groups. *A*, duration of survival. *B*, death from malignant disease

TABLE 8. *Univariate analysis p values of prognostic factors at study entry*

Factor	First Recurrence	Survival Duration*
Ta/T1 category:		
Local	0.07	0.04
Review	0.0003	0.001
Test for trend in grade 1 vs. 2 vs. 3:		
Local	0.01	0.006
Review	0.006	0.006
Primary, or 1 or less previous vs. more than 1 recurrence	0.0009	0.02
Test for trend in size less than 1 vs. 1–3 vs. greater than 3 cm.	Not significant	Not significant
Test for trend in No. tumors 1 vs. 2–3 vs. greater than 3	0.0001	Not significant

* Death from malignant disease.

tients after instillation of doxorubicin, while fever and allergic skin reaction were noted in 7 of 166 after instillation of ethoglucid. Neither leukopenia nor thrombocytopenia were seen in this study. Long-term side effects, such as a shrunken bladder, were not reported by the investigators.

DISCUSSION

Numerous randomized studies have demonstrated the advantage of adjuvant intravesical treatment after transurethral resection to decrease the recurrence rate of superficial bladder cancer compared with transurethral resection alone.[4–10] However, in 2 large studies adjuvant treatment revealed no benefit.[11,12] The inability to demonstrate a significant difference may have been due to the patients investigated,[12] treatment schedule[11] or compound used.[4] In studies comparing different intravesical cytostatics none of the drugs tested was superior to another.[13,14]

In the present study long-term differences for time to first recurrence were maintained in all patients with similar results in the subgroups with primary and recurrent tumors. For all patients the absolute benefit according to the formula, % recurrence in transurethral resection arm − % recurrence in the adjuvant treated arms, is approximately 20% for doxorubicin and 27% for ethoglucid at 3 years. The recurrence rate per year in the adjuvant treatment arms decreased to 50% of that observed with transurethral resection alone and the differences were highly significant. No differences were demonstrated between doxorubicin and ethoglucid with respect to time to first recurrence or recurrence rate.

At 5 years there was a progression in T category to worse than stage T1 disease in 14.6% of the patients, distant metastases in 4.4% and death from malignant disease in 8.8%. The values are not significantly different in the 3 arms, although the number of events is too small to draw any definitive conclusions. Since treatment of patients not in the study was at the discretion of the local investigator, 70% of all those originally allocated to transurethral resection only underwent adjuvant treatment later. Thus, adjuvant prophylactic treatment can only be compared to no or delayed treatment. After a median followup for invasion of 5 years it appeared that, of the 64 patients who had progression to stage T2 disease or worse, half had progression during the protocol treatment period, while the other half had progression during followup. Earlier reports claiming success in progression-free survival with adjuvant chemotherapy were not confirmed.[15]

The pathology review revealed considerable changes in pT category from stage pT1 to pTa disease. Muscle invasive tumors were missed in 4 of the 318 cases reviewed (1.25%). Changes in tumor grade occurred in both directions, although of the 308 cases reviewed 37 (12%) were upgraded to grade 3 and 72 (23.3%) to grade 2. Therefore, as postulated by Oosterlinck et al, it is necessary to obtain a uniform pathology review when subgroups based on T category or grade are analyzed.[10] In a separate study including data from this study a multivariate analysis of prognostic factors showed that grade of malignancy, tumor size and prior recurrence rate are the most powerful predictors of progression to stage T2 disease or greater or death from malignant disease. Patients with more than 3 previous recurrences per year, a tumor greater than 3 cm. and grade 3 malignancy had the worst prognosis.[16]

CONCLUSIONS

In regard to time to first recurrence and recurrence rate per year this European Organization for Research and Treatment of Cancer Genitourinary Group phase III trial indicates that adjuvant chemotherapy with doxorubicin and ethoglucid according to the aforementioned schedule is superior to transurethral resection alone. The study did not show that progression in stage or survival was influenced by the treatment regimen. However, progression was rarely observed and 70% of the patients who underwent resection alone re-

TABLE 9. *Patients event-free at 3, 5 or 10 years*

	% Event-Free (95% confidence interval)			% With Event (all groups)
	Doxorubicin	Ethoglucid	Control	
First recurrence at 3 yrs.	48 (40–56)	56 (48–64)	29 (17–41)	
Invasion at 5 yrs.	86 (80–92)	84 (78–90)	87 (77–96)	14.6
Distant metastases at 5 yrs.	97 (94–100)	93 (89–98)	98 (95–100)	4.4
Survival:				
All causes:				
At 5 yrs.	74 (67–81)	74 (67–81)	73 (61–84)	26.2
At 10 yrs.	46 (37–54)	53 (44–61)	42 (29–56)	
Death from malignant disease				
At 5 yrs.	92 (88–96)	88 (82–94)	97 (92–100)	8.8
At 10 yrs.	82 (75–89)	79 (71–87)	82 (70–95)	

TABLE 10. *Toxicity and cystitis*

	No. Pts. With No Complaints (%)	No. Pts. With Cystitis (%)		Total No.
		Bacterial	Chemical	
Doxorubicin	146 (83)	25 (14.2)	5 (2.8)	176
Ethoglucid	139 (83.7)	21 (12.7)	6 (3.6)	166
Totals	285 (83.3)	46 (13.5)	11 (3.2)	342

ceived adjuvant chemotherapy after leaving the study. Thus, the comparison was made between adjuvant and no or delayed adjuvant treatment.

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