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A COMBINED ANALYSIS OF EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER, AND MEDICAL RESEARCH COUNCIL RANDOMIZED CLINICAL TRIALS FOR THE PROPHYLACTIC TREATMENT OF STAGE TaT1 BLADDER CANCER

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ABSTRACT

Purpose: The use of prophylactic agents after primary resection can decrease the incidence of tumor recurrence in patients with stage TaT1 bladder cancer. However, the long-term impact on progression to muscle invasive disease as well as on duration of survival is unknown. A combined analysis of individual patient data from previously performed European Organization for Research and Treatment of Cancer (EORTC) and Medical Research Council (MRC) randomized clinical trials was done in an attempt to answer these crucial questions. We compared immediate versus no adjuvant prophylactic treatment after transurethral resection with respect to disease-free interval, time to progression to muscle invasive disease, time to appearance of distant metastases, duration of survival and progression-free survival.

Materials and Methods: All EORTC and MRC prophylactic, randomized phase III trials with primary or recurrent, stage TaT1 transitional cell bladder cancer that compared transurethral resection alone or with adjuvant prophylactic treatment were included in the study. Four EORTC and 2 MRC trials using intravesical chemotherapy or oral agents and including a total of 2,535 patients were studied.

Results: A statistically significant effect of adjuvant treatment over no adjuvant treatment was found in terms of the duration of the disease-free interval ($p < 0.01$). No clear advantage of adjuvant treatment was shown with respect to progression to invasive disease, time to appearance of distant metastases or duration of survival and progression-free survival. Median survival followup was 7.8 years.

Conclusions: Despite prologation of the disease-free interval adjuvant treatment has no apparent long-term impact on the evolution of stage TaTi bladder cancer.

KEY WORDS: bladder neoplasms, drug therapy

Stage TaT1 bladder cancer is a frequently encountered urological malignancy in clinical practice because of its high incidence (bladder cancer is the fifth most common malignancy in European men and the fourth most common in the United States, with the majority of transitional cell bladder carcinomas presenting at stage TaT1[1,2]) and high recurrence rate. After primary treatment, which usually comprises transurethral resection, 50 to 70% of patients with stage TaT1 lesions will have a recurrence.[3] Despite transurethral resection successive recurrences may increase in grade and up to 15% of patients have progression to muscle invasive disease (greater than stage T1) with a subsequent poor prognosis.[4]

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It has been shown that the prophylactic use of certain agents, mainly via local instillation into the bladder, can decrease the incidence of tumor recurrence after primary resection.[5] At least 35 different agents, including cytotoxic drugs, immunomodulators and vitamins, have been used by the intravesical or oral route for adjuvant prophylaxis of stage TaT1 bladder cancer. Only a few of these agents have been effective, including thiotepa, epodyl, doxorubicin, mitomycin C, epirubicin and bacillus Calmette-Guerin (BCG). Other agents, including interferon, interleukin, mitoxantrone and bropirimine, are currently under investigation.

During the last 15 years the European Organization for Research and Treatment of Cancer (EORTC) Genitourinary Tract Cancer Cooperative Group as well as the Medical Research Council (MRC) working party on superficial bladder cancer have performed a series of randomized phase III studies investigating the prophylactic treatment of stage TaT1 bladder cancer. Many studies have demonstrated the advantage of adjuvant prophylactic treatment after transurethral resection compared to transurethral resection alone in decreasing the recurrence rate or in prolonging the disease-free

interval of patients with stage TaT1 bladder cancer.[6-12] However, they failed to demonstrate the definitive superiority of 1 agent over another.[13-15] There also is no evidence that adjuvant prophylactic treatment is of long-term benefit compared to transurethral resection alone in terms of time to muscle invasive disease and duration of survival. These 2 crucial end points cannot generally be assessed in individual trials because only 10 to 15% of patients entered in such trials can be expected to have progression. Despite long-term followup, individual trials have only a low power to detect medically plausible differences with respect to muscle invasion and death.

A possible way to overcome this problem is to perform a combined analysis of completed trials using meta-analysis techniques, a formal statistical methodology used to combine the results of separate but similar studies in a quantitative manner.[16] The statistical power of the tests used to compare treatments is increased by using all of the evidence from a number of randomized trials, rather than only 1. These techniques may be used in an attempt to draw conclusions concerning the short-term and long-term benefits of different therapeutic options in the treatment of stage TaT1 bladder cancer.

The objectives of our combined analysis of EORTC and MRC trials are to compare the use of transurethral resection alone or with adjuvant prophylactic treatment with respect to the disease-free interval, time to progression to muscle invasive disease, time to appearance of distant metastases, duration of survival (all causes of death and death from malignant disease) and progression-free survival. Patients were randomized to adjuvant prophylactic treatment or no adjuvant prophylactic treatment groups. At recurrence the treatment that the patient was initially randomized to receive was generally begun again after transurethral resection, and patients were followed for further recurrence. However, patients were eventually withdrawn from the original treatment at subsequent recurrences and further therapy was given at the discretion of the investigator. Therefore, for long-term end points, such as invasion and death, it should be noted that patients in the no adjuvant treatment group often were likely to have received delayed adjuvant treatment. Exactly how many patients never received intravesical treatment is unknown.

MATERIAL AND METHODS

Selection criteria. Trials performed by the EORTC and MRC were eligible for inclusion in this combined analysis only if they were randomized, phase III studies assessing the adjuvant prophylactic treatment of primary or recurrent stage TaT1 transitional cell bladder cancer. Trials had to compare transurethral resection alone or with adjuvant prophylactic treatment, and long-term followup for invasion and death was mandatory, including studies with cytotoxic drugs or oral agents that were used as adjuvant prophylactic treatment. No trials with BCG were included in the analysis because neither the EORTC nor the MRC conducted any trials in which transurethral resection alone was compared to transurethral resection plus BCG. Six randomized controlled trials (4 EORTC and 2 MRC, total 2,535 patients) met the trial selection criteria (table 1).[6-12]

Data collection. Individual data for all randomized patients, including those who were ineligible, were used in the analysis. Updated followup information on the end points defined was collected by the EORTC. One of us (A. P.) reviewed all patient data and visited the different institutions to collect patient data when necessary. Thus, the data presented are more recent than those previously reported in the individual studies.

For all patients the baseline data collected included the date of randomization, treatment given, patient age, sex, tumor status (primary or recurrent), prior recurrence rate, prior intravesical treatment, T category, grade (local and review pathology result), carcinoma in situ, and number and size of tumors. Tumor stage and grade were assessed in accordance with the 1974 TNM classification, confirmed in 1978.[17] In trial 30751 no information on patient sex or whether the tumors were stage Ta or T1 was collected.

TABLE 1. *EORTC and MRC trials included in the combined analysis*

Trial No.	Drugs Used	Total No. Pts.	No. Controls
EORTC:			
30751[6]	Thiotepa, VM-26	370	124
30791[8]	Doxorubicin, epodyl	443	73
30863[7]	Epirubicin	512	255
30781[9]	Pyridoxine (oral)	291	144
MRC:			
BSO1[10,11]	Thiotepa	417	139
BSO3[12]	Mitomycin C	502	171
Total No. pts.		2,535	906

Criteria of evaluation and definition of end points. While the primary end point to assess the long-term results was progression-free survival, patients were assessed with respect to 7 end points: 1) time to first recurrence (disease-free interval)—time from randomization to the date of the first bladder recurrence (patients without recurrence were censored at the date of the last available followup cystoscopy), 2) time to progression to muscle invasive disease—time from randomization until progression to stage T2 or greater cancer in the bladder (patients without muscle invasion were censored at the date of the last available followup cystoscopy), 3) time to distant metastases—time from randomization until the first appearance of distant metastases (patients without distant metastases were censored at the date of the last physical examination), 4) time to a second primary tumor—time from randomization until the first appearance of a second primary tumor (patients without a second primary were censored at the date of the last physical examination), 5) duration of survival (all causes of death)—time from randomization until death (patients still alive or lost to followup were censored at the last date they were known to be alive), 6) duration of survival (death from malignant disease)—time from randomization until death from malignant disease (not necessarily bladder cancer, patients still alive or lost to followup were censored at the last date they were known alive, and those who died of nonmalignant causes were censored at death) and 7) progression-free survival—time from randomization to muscle invasion, distant metastases, second primary or death from malignant disease, whichever occurred first. Otherwise patients were censored at the last date they were known to be alive.

Statistical considerations. The statistical analysis software was used. Analyses were performed on an intent to treat basis, that is patients were analyzed according to the allocated treatment, regardless of whether or not they actually received that treatment. Treatment effects were compared only within a trial, following the basic "compare like with like" principle.[18]

Within each separate trial the "observed minus expected" number of events and its variance were calculated based on a comparison of the treatment groups using a log-rank test.[18,19] For an assessment within a stratum or subgroup observed minus expected values from each trial within the subgroup were added. Likewise, the variance was the sum of the individual variances of each observed minus expected value within a subgroup. Finally, the overall results were assessed by adding the totals of the observed minus expected values and variances over all subgroups and trials.

To present the results graphically hazard ratios, that is exp(observed minus expected/variance), with 95% confidence

intervals were calculated.[18] The hazard ratio represents the overall risk of an event in the treated group compared to the no treatment group. A hazard ratio of 1 indicates no difference in treatment efficacy, less than 1 favors the treated group and more than 1 favors the no treatment group. For example a hazard ratio of 0.90 represents a 1 − 0.90 = 10% decrease in the risk of the event in the treated group.

In the graphs (forest plots), the hazard ratio and confidence interval for each individual study are represented by a black square and a horizontal line, while the hazard ratio and confidence interval for a combination of several trials is plotted as a diamond shape. The percent decrease or increase in the hazard ratio was also calculated along with its standard deviation.

Time to event distributions (disease-free interval, time to progression to muscle invasive disease, duration of survival and so forth) were estimated using the Kaplan-Meier method[20] and compared using the log-rank test stratified by study.[19] When there was a natural ordering (for example age groups) a trend test was used to test for a trend of difference in treatment effect on the hazard ratios in the ordered groups.[21] Chi-square tests for heterogeneity and interactions were used to detect differences among trials.[21] All p values referred to are 2-sided, since it could not be ruled out that the intravesical treatment might produce worse results.

The average absolute benefit at a given point in time t was estimated as the absolute difference between the Kaplan-Meier estimate in the transurethral resection only group at time t and the estimate in the treated group at time t based on the estimated hazard ratio under the assumption of proportional hazards. The 95% confidence interval for the average absolute survival benefit was calculated based on the same technique using the 95% confidence interval for the hazard ratio. Median followup was calculated based on the Kaplan-Meier estimate of the median when patients were censored at the time of the event.

RESULTS

Patient characteristics. Patient and tumor characteristics, including the distribution of the T category and grade, as well as the number and size of tumors at entry into the study, are given in table 2. Patients tended to have primary, solitary stage Ta tumors smaller than 2 cm. in diameter. Thus, the risk of recurrence and/or progression in the patients included in our combined analysis was relatively low. Only during more recent years were detailed prognostic factor analyses performed that allowed for classification of patients into risk groups of good, intermediate and poor prognoses. Although the high risk category is the most interesting, a separate analysis of these patients would greatly decrease the number of patients who could be included, thus weakening the strength of the evidence.

Of the patients studied 12% retrospectively were found to be ineligible mainly because in a number of trials the histological results only became available after entry into the study. Thus, in a number of patients either no tumor (stage T0G0) or muscle invasive disease (greater than stage T1) was found. In some cases no data were available. The few studies reporting previous treatment mainly included prior transurethral resections.

The incidence of recurrence, muscle invasion, distant metastases, second primaries, number of cystectomies, patient survival status as of January 1995 and cause of death are given by treatment arm in table 3. The tables are purely descriptive in nature and should not be used for comparison purposes, since they do not consider duration of followup.

Effects of prophylactic treatment in all randomized patients. Treatment efficacy comparisons are based on all 2,535 patients randomized. However no followup data were available for 135 patients. Median followup was 4.6 years for the disease-free interval, 5.5 years for invasion and 7.8 years for survival (maximum 18.2).

Figure 1, *A* shows the disease-free interval curves according to adjuvant versus no adjuvant treatment groups. The

TABLE 2. *Patient characteristics*

	No. Pts. (%)
Total No. pts.	2,535 (100)
Eligible:	
Yes	2,240 (88)
No	295 (12)
Sex:	
Male	1,607 (63)
Female	520 (21)
Not assessed	408 (16)
Tumor status:	
Primary	1,950 (77)
Recurrent	444 (18)
Unknown	141 (5)
Prior treatment:	
No	2,310 (91)
Yes	83 (4)
Unknown	142 (5)
T category:	
T0	53 (2)
Ta	1,244 (49)
Ta or T1	370 (15)
T1	668 (26)
More than T1	76 (3)
Unknown	124 (5)
Grade:	
0	53 (2)
1	1,183 (47)
2	871 (34)
3	316 (12)
Unknown	112 (4)
No. tumors:	
0	14 (1)
1	1,686 (67)
2–5	590 (23)
More than 5	139 (5)
Unknown	106 (4)
Size of tumor (cm.):	
0	15 (1)
Less than 2	1,155 (46)
Less than 4	905 (36)
Less than 6	261 (10)
6 or More	71 (3)
Unknown	128 (5)

Patient age ranged from 14 to 100 years (median 64).

TABLE 3. *Treatment results*

	No. Treatment (%)	No. No Treatment (%)	Total No. Pts. (%)
Total No. pts.	1,629 (100)	906 (100)	2,535 (100)
Recurrence:			
Yes	766 (47)	477 (53)	1,243 (49)
No	863 (53)	429 (47)	1,292 (51)
Muscle invasion:			
Yes	189 (12)	80 (9)	269 (11)
No	1,440 (88)	826 (91)	2,266 (89)
Distant metastases:			
Yes	74 (5)	34 (4)	108 (4)
No	1,555 (95)	872 (96)	2,427 (96)
Second primary:			
Yes	93 (6)	48 (5)	141 (6)
No	927 (57)	548 (61)	1,475 (58)
Unknown	609 (37)	310 (34)	919 (36)
Cystectomy:			
Yes	161 (10)	75 (8)	236 (9)
No	1,468 (90)	831 (92)	2,299 (91)
Survival:			
Alive	1,001 (61)	625 (69)	1,626 (64)
Dead	628 (39)	281 (31)	909 (36)
Cause of death:			
Malignant disease	229 (36)	93 (33)	322 (35)
Infection	55 (9)	20 (7)	75 (8)
Cardiovascular disease	209 (33)	101 (36)	310 (34)
Other chronic disease	16 (3)	4 (2)	20 (2)
Other	41 (7)	26 (9)	67 (7)
Unknown	78 (12)	37 (13)	115 (13)

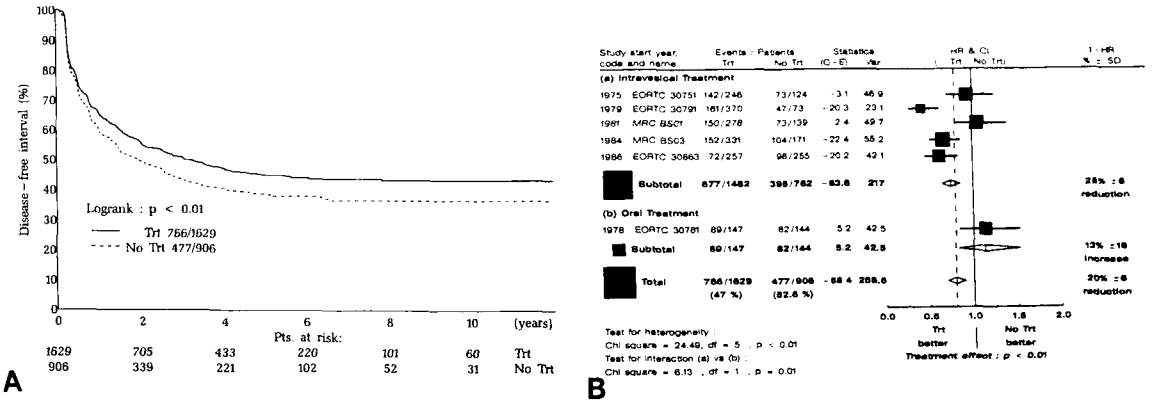

FIG. 1. Kaplan-Meier curves (*A*) and forest plot (*B*) of time to first recurrence (disease-free interval) by treatment group

difference in the disease-free interval in favor of treatment is statistically significant ($p < 0.01$). The hazard ratio of treatment versus no treatment for all trials was 0.8, which is equivalent to a mean plus or minus standard deviation 20 ± 6% decrease in the risk of recurrence in the treated group compared to the no treatment group. For example, the estimate of the average absolute benefit in the percentage of patients disease-free at 8 years for those randomized to receive adjuvant treatment was 8.2% (44.9 versus 36.7%) with a 95% confidence interval of 3.8 to 12.5%. Figure 1, *B* shows the hazard ratios for the disease-free interval according to the treatment group and type of treatment (intravesical or oral).

The time to progression to muscle invasive disease in the 2 treatment groups is shown in figure 2, *A*. No statistically significant difference in this parameter was observed, if anything with a trend in favor of the no treatment group. The hazard ratio of treatment versus no treatment for the time to progression to muscle invasive disease was 1.19, which is equivalent to a mean 19 ± 15% increase in the risk of invasion in the treated group compared to the no treatment group (fig. 2, *B*). While this difference may seem great, it corresponds for example to an estimated absolute decrease of 1.95% (89.03 versus 87.08%) in the percentage of patients invasion-free at 8 years in the treated group, with a 95% confidence interval from a 0.88% increase to a 5.5% decrease.

No statistically significant difference in the overall duration of survival (fig. 3, *A*) and the time to death due to malignant disease was observed between the 2 treatment groups.The hazard ratios of treatment versus no treatment were 1.1 for overall survival (fig. 3, *B*) and 1.21 for death from malignant disease, which is equivalent to a 10 ± 8% and 21 ± 13% increase, respectively, in the risk of death in the treated compared to the no treatment group. The cause of death is given in table 3.

Progression-free survival curves are shown in figure 4, *A*. No statistically significant difference in the duration of progression-free survival between the 2 treatment groups was observed. Figure 4, *B* shows the hazard ratios for progression-free survival according to the 2 different treatment groups. The hazard ratio of treatment versus no treatment was 1.08, which is equivalent to an 8 ± 10% increase in the risk of progression or death in the treated group compared to the no treatment group. No statistically significant differences were noted between the 2 treatment groups in the time to distant metastases (fig. 5, *A*) and time to a second primary, which was assessed only in the EORTC patients (fig. 5, *B*).

A separate analysis performed in only the primary patients (newly diagnosed disease) yielded results similar to those cited. The hazard ratios and corresponding p values for these patients were 0.81 ± 6% ($p < 0.01$) for disease-free interval, 1.09 ± 17% ($p > 0.1$) for time to muscle invasion, 1.10 ± 9% ($p > 0.1$) for duration of survival and 1.03 ± 12% ($p > 0.1$) for progression-free survival.

DISCUSSION

Our results confirm the favorable impact of adjuvant prophylactic treatment on the disease-free interval of patients with stage TaT1 bladder cancer. However, our analyses have shown no evidence that prophylactic treatment is of long-term benefit compared to transurethral resection alone in terms of time to invasive disease, or duration of survival or

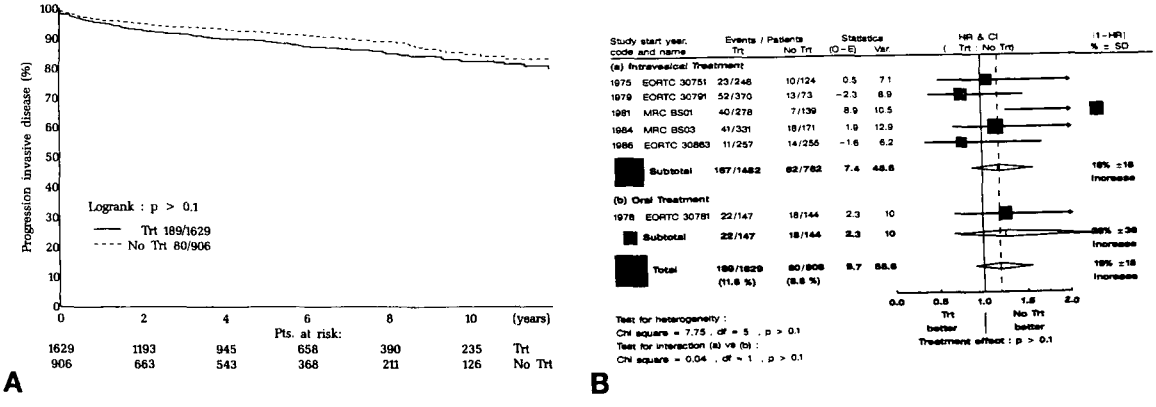

FIG. 2. Kaplan-Meier curves (*A*) and forest plot (*B*) of time to progression to muscle invasion by treatment group

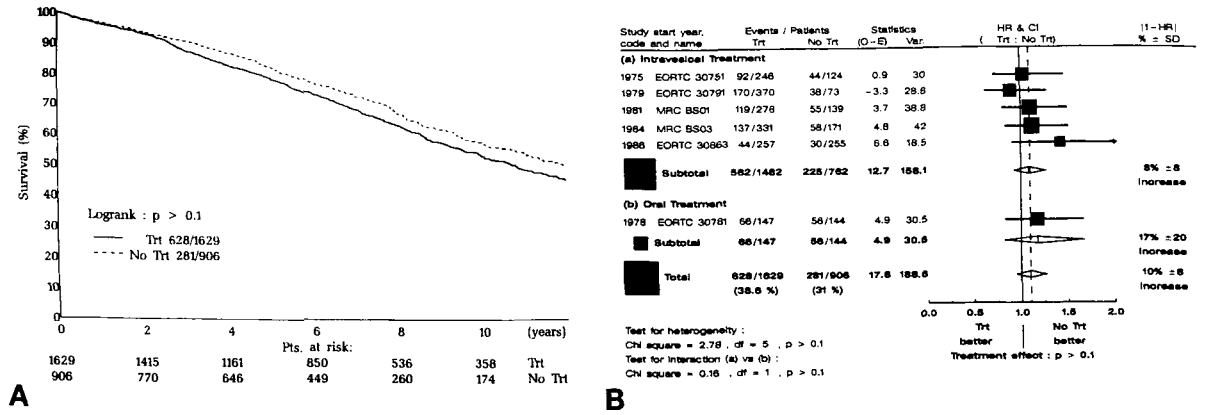

FIG. 3. Kaplan-Meier curves (*A*) and forest plot (*B*) of duration of overall survival by treatment group

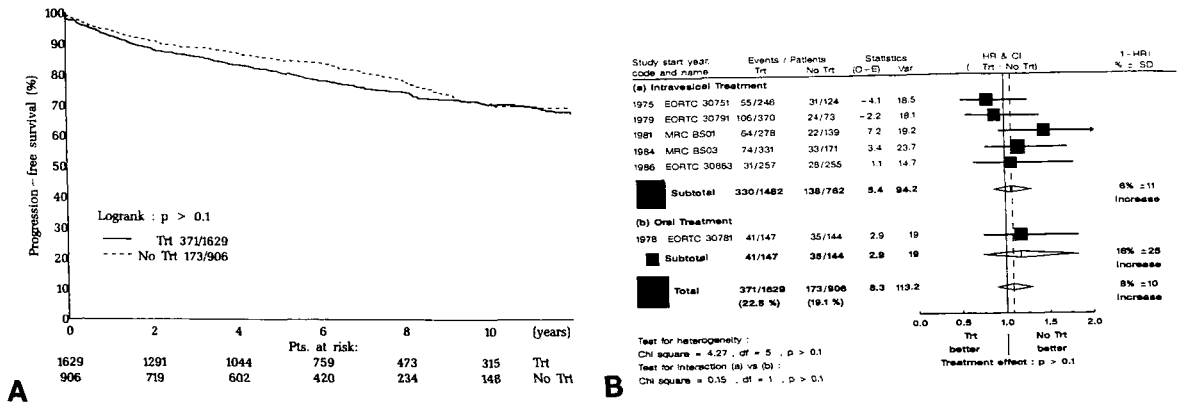

FIG. 4. Kaplan-Meier curves (*A*) and forest plot (*B*) of duration of progression free survival by treatment group

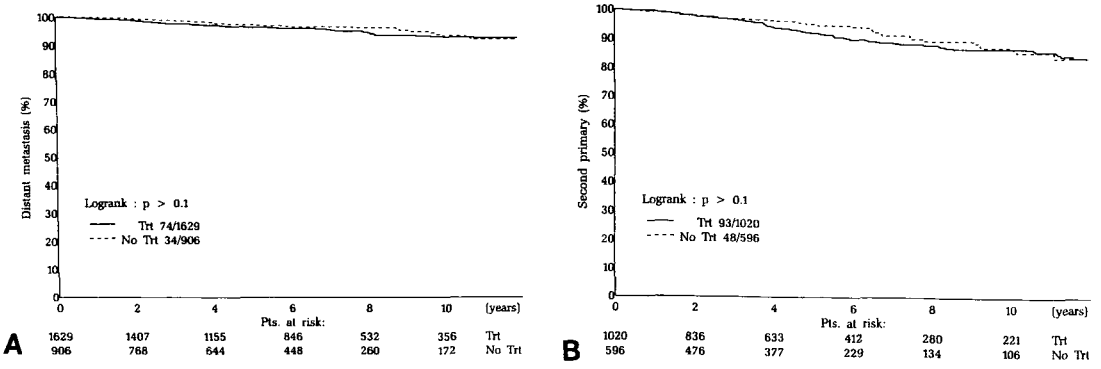

FIG. 5. Kaplan-Meier curves of time to distant metastases (*A*) and time to second primary (*B*) by treatment group

progression-free survival. No differences were observed in the incidence of second malignant tumors in the treatment groups. Based on this finding there is no evidence, as suggested by some,[22-24] of a possible carcinogenic effect locally on the epithelium or systemically of intravesical chemotherapy. Other reasons not related to intravesical treatment should be considered to explain the high incidence of second tumors among patients with stage TaT1 bladder cancer.

No significant differences were detected with respect to these end points despite the analysis of approximately 2,500 patients and a median followup for survival of 7.8 years. While the total number of patients with invasion (269) and death from malignant disease (322) remained relatively small, accounting for only slightly more than 10% of the patients followed, the power to detect slight but plausible treatment differences of 5% is approximately 95%, with the 95% confidence interval for the difference in the percentage of patients free of muscle invasion at 8 years in the treated group ranging from a 0.88% increase to a 5.5% decrease.

Our results might be criticized from several different viewpoints. Criticism might be raised as to the heterogeneity of the patients and the trials included. The trials included in the analysis evaluated 7 different drugs and varied according to the mode of administration (intravesical or oral), dose, duration of instillations, interval between instillations and duration of treatment. Primary and recurrent cases were included, with trials also varying according to the prognosis of the patients. The use of proper meta-analysis techniques

overcomes some of these criticisms by only comparing treatment results within a given trial and then combining the results across all trials to obtain an average result. The statistical heterogeneity of results across trials is assessed and at no time are patients in different trials being compared. A separate analysis with similar results was done in the primary patients, since this was the subgroup of greatest interest. The only trial assessing oral treatment was analyzed in a separate stratum in the forest plots so that the intravesical chemotherapy trials can be considered separately if so desired.

The long-term results for invasion and survival might be criticized due to the lack of a pure "no treatment arm." Because patients going off study for recurrence were treated with intravesical treatment at the discretion of the investigator, adjuvant prophylactic treatment can be compared only to no or delayed treatment, thus, possibly diluting the size of the treatment effect, that is the data were analyzed based on the intent to treat principle. Thus, the results should be interpreted in this light, that is of comparing immediate to delayed treatment. Even if patients who never received adjuvant treatment could have been accurately identified, a separate subgroup analysis in these patients would have been biased.

Intravesical BCG was not addressed in this combined analysis. No trials were conducted in the EORTC or the MRC in which transurethral resection alone was compared to transurethral resection plus BCG. However some investigators would consider intravesical BCG and not chemotherapy to be the first line treatment of choice in the adjuvant therapy of stage TaT1 bladder cancer, particularly in high risk cases (recurrent, multifocal stage T1G3 disease, carcinoma in situ and so forth).[25–32] In several randomized phase III trials BCG was compared to intravesical chemotherapy, predominently in high risk patients.[25,29,32] Most of these trials indicated the superiority of BCG over chemotherapeutic agents with respect to the recurrence rate.

Some studies suggested that BCG prevents tumor progression, delays cystectomy and prevents death from bladder cancer.[25–27] In an EORTC trial that included 361 patients, no significant differences were noted in the comparison of BCG and mitomycin C.[15] However, in this trial relatively few patient with high risk tumors were included and 45% had a recurrence. It would be interesting to perform a meta-analysis of all randomized trials comparing transurethral resection plus BCG to transurethral resection alone or with intravesical chemotherapy. Such an analysis could answer the question of whether intravesical BCG is more effective than intravesical chemotherapy, which does not improve long-term survival.

CONCLUSIONS

Adjuvant prophylactic treatment as given in the studies included in our combined analysis has a favorable effect over no (delayed) prophylactic treatment in terms of the duration of the disease-free interval. Despite a 7.8-year median followup, this short-term effect has not been translated into a long-term benefit. No significant advantage of prophylactic treatment has been shown with respect to the time to progression to muscle invasive disease, time to appearance of distant metastases, second primary tumor or duration of survival. A separate analysis in only patients with newly diagnosed disease yielded similar results. Based on this analysis it is clear that, while the long-term prognosis of stage TaT1 bladder cancer patients remains good, use of adjuvant prophylactic treatment has little apparent effect on the long-term results and new modes of treatment should be developed.

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EDITORIAL COMMENTS

Previous studies have failed to show a statistically significant long-term decrease in tumor recurrence in patients treated with intravesical chemotherapy. The authors of this monumental study should be complimented for demonstrating that intravesical chemotherapy does clearly provide a lasting decrease in the incidence of tumor recurrence. The crude reduction in tumor recurrence is only 6% (from 53% recurrence without treatment to 47% with treatment, table 3 in article) but hazard ratio estimates project a 20% overall decrease in risk of tumor recurrence with intravesical chemotherapy and an estimated 8% decrease in tumor recurrence at 8 years. The importance of this 20% decrease in the risk of tumor recurrence to patients with bladder cancer should not be underestimated because tumor recurrence has psychological as well as physical consequences.

Previous studies have failed to show a decrease in disease progression or mortality following intravesical chemotherapy. Unfortunately, it appears clear that the decrease in tumor recurrence with chemotherapy is not associated with any decrease in disease progression or mortality. As noted in this study, if anything, the trend is in favor of the no treatment groups. It should be emphasized that this trend is not statistically significant but, nonetheless, it is of some concern. Referring, for example, to the data in table 3 in the article, if the same ratio of muscle progression in the no treatment groups (80 of 906 patients) is applied to the treatment groups with 1,629 patients, the expected incidence of muscle invasion would be 143, which is 46 patients less than the observed 189 patients. Similarly, the apparent decrease in survival from 69% in the no treatment groups to 61% in the treatments groups, although statistically insignificant, is still disconcerting, particularly because of the apparent increase in death from malignant disease (93 of 906 no treatment patients, or 10.3%, compared to 229 of 1,629 treatment patients, or 14.1%, or an excess of malignant deaths of 62 patients). These numbers again are not statistically significant and, therefore, they must be taken with a grain of salt but we must not conclude that studies have proved the opposite, that chemotherapy cannot promote disease progression in some patients. More simply, chemotherapy is now known to decrease long-term recurrence but not disease progression or mortality. The effect, if any, of chemotherapy on disease progression is so slight that thousands of study patients would be needed to achieve statistical significance. Such refinements in our knowledge of bladder cancer treatment clearly depend on cooperative groups. The EORTC and MRC are premier examples of how group cooperation can advance the treatment of urological cancer.

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This combined analysis of the EORTC and MRC randomized clinical trials of adjuvant chemotherapy in stage TaT1 bladder cancer is a major contribution. I wish to comment on selected aspects of what has been learned as they relate to the basis for assessing the efficacy or obtaining regulatory approval of agents for the adjuvant treatment of stage TaT1 bladder cancer.

For a number of years there has been debate about whether end points related to time to first recurrence are suitable outcomes for evaluating the efficacy of adjuvant treatments for stage TaT1 bladder cancer.[1,2] For example, the United States Food and Drug Administration approved the use of BCG for carcinoma in situ based on a response to therapy outcome but explicitly did not approve the adjuvant use of BCG in stage TaT1 bladder cancer despite strong data showing that BCG prolonged the recurrence-free interval.[3] This denial of approval for use of BCG in the adjuvant treatment in stage TaT1 disease was based on concern about whether a net patient benefit existed when the advantage in recurrence related outcome was balanced against side effects and convenience factors.

Two arguments have been made in favor of using recurrence related outcomes: 1) a delay in recurrence is a surrogate for delay in longer term outcomes, such as progression or death and 2) a delay in recurrence represents a direct or net patient benefit. The surrogacy argument has been difficult to support from data because it has not been possible to show a strong relationship between delay in recurrence and time to progression or death. The authors fail to show that there is a relationship between recurrence and progression or death although the sample size and number of events are large. As a result, it will now be even more difficult to argue that an advantage

in recurrence related outcomes translates to a long-term patient benefit.

Unfortunately, the authors also do not provide data supporting the argument that an advantage with respect to recurrence related outcomes represents a patient benefit. A convincing demonstration that an advantage in recurrence related outcomes translates to a patient benefit would at a minimum need to include data on side effects, and also ideally include data on patient inconvenience factors, impact on quality of life and pharmacoeconomics. These additional data are necessary to assess the net patient benefit. Thus, while we are again provided strong evidence that the adjuvant treatment of stage TaT1 bladder cancer significantly delays recurrence, we continue to be in a data-free zone with respect to knowing whether this consistently demonstrable delay in recurrence has a net worth to the patient.

Will we ever have a generally applicable answer to the net patient benefit question? A study designed to gather the data necessary to evaluate the net patient benefit would be complex and long. More importantly, such a study may not yield a clear answer because the evaluation of net patient benefit will depend heavily on individual patient opinion. Specifically, such a study would have to be carefully designed with respect to the quality of life component because the impact on quality of life would likely be viewed differently by different patients. Some patients may prefer to cope with the inconveniences and side effects associated with delaying recurrence, whereas others would not. Therefore, the quality of life component of such a study would need to include methodology for assessing health state preferences, which is complex and controversial.[4,5] This heavy dependence on individual patient opinion is unique to the adjuvant treatment of stage TaT1 bladder cancer and not similar to other cancers. It is more similar to the situation for treatment of some type of episodically recurring chronic diseases, such as multiple sclerosis.

What, then, should the clinicians and regulatory agencies use as the basis for assessing the efficacy of adjuvant agents in stage TaT1 bladder cancer? The extreme would be to require hard data from a study designed to quantify a net patient benefit. It is argued in this study that it is unlikely that such data will ever become available because of the nature of adjuvant treatment for stage TaT1 bladder cancer and the type of data required, specifically the assessment of health preference states. Therefore, evidence of efficacy will probably need to be based on the (easily) demonstrable advantage in recurrence related outcomes together with data characterizing side effects, and the assumption that patients and physicians will have to make the adjuvant treatment decision based on the projected net benefit of adjuvant therapy. In any given situation this decision would be based on an assessment of the data available on recurrence delay and side effects together with highly individualized projections of the impact on quality of life and convenience factors. (In the case of BCG, consideration might also have to be given to the public health impact of its broader use, such as whether antibiotic treatment of BCG side effects or the prophylactic use of antibiotics in patients being treated with BCG leads to tuberculosis control problems.)

Thus, a significant contribution of this study has been to free us further from the notion that an advantage in recurrence related outcomes can be argued to portend an advantage in longer term outcomes, at least when the agents under study are not used in a schedule similar to those reported. Freeing us from this notion forces us to think about direct and net patient benefits. We are left with the question of whether there should be an attempt to perform the difficult study that would depend on using health state preference methodology. Would such a study be cost-effective? Would there be a high likelihood of a definitive answer? If we do not do a formal assessment of net patient benefit, then we have only the type data currently available combined with patient and physician judgment to guide adjuvant treatment decisions.

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REPLY BY AUTHORS

We agree with the comments of Lamm and Blumenstein. We wish to emphasize that this combined analysis mainly concerns good risk patients and it must be remembered that many, probably most, in the no adjuvant treatment group did eventually receive intravesical treatment after recurrence. It is unknown to what extent the impact of delayed adjuvant treatment may have had on progression or survival. Thus, the results of the combined analysis should be interpreted in this light.

Due to the nature of stage TaT1 bladder cancer, the problem of assessing net patient benefit and the choice of meaningful end points for evaluating treatment effectiveness are particularly important questions. As discussed by Blumenstein, there are no easy answers to this question. The question of the importance of individual patient opinion is not unique to superficial bladder cancer but this disease does provide a unique setting in which to study this question. Aware of this fact, the EORTC is developing a quality of life module specific to stage TaT1 bladder cancer, which will be used in our next adjuvant trial. Regardless of the results of a trial incorporating quality of life or health state preference methodology, it is essential that future patients be able to make an informed decision about their treatment based on objective data from large scale randomized trials and meta-analyses along with their own personal preferences. The results of this combined analysis will hopefully act as a stimulus to promote further work in these fields.