# Prevention of Recurrence With Epirubicin and Lactobacillus Casei After Transurethral Resection of Bladder Cancer

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**Purpose:** A prospective, randomized, controlled trial was done to evaluate whether oral administration of a preparation of the probiotic agent Lactobacillus casei (Yakult Honsha, Tokyo, Japan) could enhance the prevention of recurrence by intravesical instillation of epirubicin after transurethral resection for superficial bladder cancer.

**Materials and Methods:** Between August 1999 and December 2002, 207 patients clinically diagnosed with superficial bladder cancer were included as study candidates and underwent transurethral resection, followed by intravesical instillation of 30 mg epirubicin/30 ml saline twice during 1 week. After histological confirmation of superficial bladder cancer they were again included as study participants with 102 randomized to receive treatment with 6 additional intravesical instillations of epirubicin during the 3-month period after transurethral resection (epirubicin group) and 100 randomized to intravesical chemotherapy on the same schedule as the epirubicin group plus oral administration of 3 gm Lactobacillus casei preparation per day for 1 year (epirubicin plus Lactobacillus casei group). Patients were evaluated for intravesical recurrence, disease progression, prognosis and adverse drug reactions.

**Results:** The 3-year recurrence-free survival rate was significantly higher in the epirubicin plus Lactobacillus casei group than in the epirubicin group (74.6% vs 59.9%, $p = 0.0234$), although neither progression-free nor overall survival differed between the groups. The incidence of adverse drug reactions did not significantly differ between the groups and there were no serious adverse drug reactions.

**Conclusions:** Intravesical instillation of epirubicin plus oral administration of Lactobacillus casei preparation is a novel, promising treatment for preventing recurrence after transurethral resection for superficial bladder cancer.

*Key Words: bladder; bladder neoplasms; neoplasm recurrence, local; epirubicin; Lactobacillus casei*

Although superficial bladder cancer can be treated with TUR, the high frequency of intravesical recurrence is a concern. It was reported that intravesical recurrence develops in 50% to 70% of patients within 5 years after TUR for superficial bladder cancer and the risk of progression to invasive cancer is 5% to 20%.[1] The recurrence risk peaks in the early postoperative phase at 100 to 120 days after TUR for multiple tumors and at 350 to 440 days after TUR for a solitary tumor, and then it decreases to and continues at a stable level for a long period.[2] Intravesical instillation therapy using anticancer agents or BCG has been developed to prevent intravesical recurrence of superficial bladder cancer after TUR. Intravesical instillation of mitomycin C, doxorubicin or EPI-ADM was reported to decrease the short-term (1 to 3-year) recurrence rate by about 20%.[3] On the other hand, intravesical instillation of BCG has stronger efficacy for preventing recurrence than anticancer agents, although the incidence and severity of adverse effects are higher with it than with chemotherapy.[4] Therefore, BCG is reserved for patients with high risk superficial bladder cancer, while anticancer agents are used in patients with intermediate risk cancer.

The LC preparation used in the study was a powdered preparation containing about $1 \times 10^{10}$ cells of LC Shirota strain per gm. In Japan LC preparation has been safely used as a probiotic agent for more than 30 years. When it is orally administered, the LC preparation was reported to act as an immunomodulator through the intestinal tract and potentiate antitumor responses in mice.[5] Intravesical instillation of heat killed cells of the LC Shirota strain was also shown to exert antitumor effects in mice with bladder cancer and prevent bladder cancer.[6] In a randomized, comparative clinical trial Aso et al reported that the 50% recurrence-free interval after TUR for superficial bladder cancer was significantly prolonged by oral LC preparation to 1.8 times that in a control group.[7] They also performed a placebo controlled, double-blind clinical trial and noted that treatment with LC preparation was safe and effective for preventing intravesical recurrence after TUR for superficial bladder cancer.[8]

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Study received local institutional review board approval.
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These reports suggest that LC preparation can prevent intravesical recurrence after TUR for superficial bladder cancer through a mechanism different from that of intravesical chemotherapy.

Therefore, we planned a randomized, controlled trial in patients with superficial bladder cancer at intermediate risk for recurrence to evaluate whether postoperative oral administration of LC preparation could enhance the prevention of recurrence by intravesical instillation chemotherapy with EPI-ADM after TUR for superficial bladder cancer.

## MATERIALS AND METHODS

This study was a multicenter, prospective, nonblinded, randomized, controlled trial. Patients were considered eligible if they had clinical stage Ta or T1, grade 1 or 2 primary or recurrent transitional cell carcinoma and the tumors appeared to have been eliminated completely by TUR. Patients meeting any of certain criteria were excluded from study, including a primary single Ta grade 1 tumor, grade 3 tumor, multiple recurrent tumors, history of urothelial carcinoma of the upper urinary tract, history of intravesical instillation of EPI-ADM or BCG, history of intravesical instillation of any agents during the 4-week period preceding the study, other active neoplasms or serious medical conditions. LC strain is contained in a fermented milk drink such as Yakult (Yakult Honsha, Tokyo, Japan) or a fermented milk product such as yogurt as an intestinal remedy. Therefore, patients regularly ingesting such beverage, food or drug containing LC strains were also excluded.

Before treatment patients provided a history and underwent physical examination, urinalysis, urine cytology examination, complete blood count, blood urea nitrogen and serum creatinine determination, liver function tests and electrocardiography. Chest x-rays and excretory urography were also performed. At study entry no patients had evidence of residual tumor on endoscopic examination and urine cytology.

Patients were added to the study via fax using a 2-step method at the Kyushu University Urological Oncology Group Data Center. After providing informed consent in writing patients were documented as study candidates before TUR for superficial bladder cancer. A 30 mg dose of EPI-ADM dissolved in 30 ml physiological saline was instilled into the bladder through a sterile catheter immediately after (within 2 hours) and 1 week after TUR. Patients were instructed not to void for 2 hours after instillation. When confirmed to be eligible based on the results of histopathological examination of resected tumor specimens, patients were again included as study participants and randomly assigned to receive treatment with 6 additional intravesical instillations of EPI-ADM during the 3-month period after TUR (EPI-ADM group) or intravesical chemotherapy on the same schedule as the EPI-ADM group plus 3 gm oral LC preparation per day (EPI-ADM plus LC group). Intravesical instillation of EPI-ADM was administered 3, 4, 6, 8, 10 and 12 weeks after TUR. The LC preparation dose was determined according to trials by Aso et al, in which the efficacy and safety of 3 gm oral LC per day were observed.[7,8] Figure 1 shows the group treatment schedules. Administration of the LC preparation was begun within 2 weeks after randomization and continued for 1 year.

In each groups urinalysis and cytological examination of urine samples were performed monthly for 3 months after TUR, every 3 months in the first 2 years and at 6-month intervals thereafter. Cystoscopy was performed every 3 months in the first 2 years and at 6-month intervals thereafter. Local and systemic toxicity was also monitored. Routine laboratory tests (hematology and biochemistry) were performed before, and 1, 3, 6, 9 and 12 months after TUR. All patients were followed at least 3 years and the treatment method after the first recurrence was at the discretion of each investigator. The severity of adverse reactions was assessed according to Common Terminology Criteria for Adverse Events, version 2.0.

The primary end point of this trial was the intravesical recurrence-free survival rate. Recurrence was defined as positive findings on cystoscopy or consecutive positive findings on urine cytology. Positive findings on cystoscopy were confirmed histologically by biopsy or TUR. Secondary end points were the progression-free survival rate, the overall survival rate, and the incidence and severity of adverse drug reactions. Progression was defined as muscle invasive bladder cancer or metastasis. Intravesical recurrence-free, progression-free and overall survival was defined as the interval from TUR to each event or the last followup without an event. Observation was concluded on January 31, 2006.

Sample size was calculated as described. Assuming that the 3-year recurrence-free survival rate would be 55% and 75% in the EPI-ADM and EPI-ADM plus LC groups, respectively, 92 patients per group were required to detect a 20%

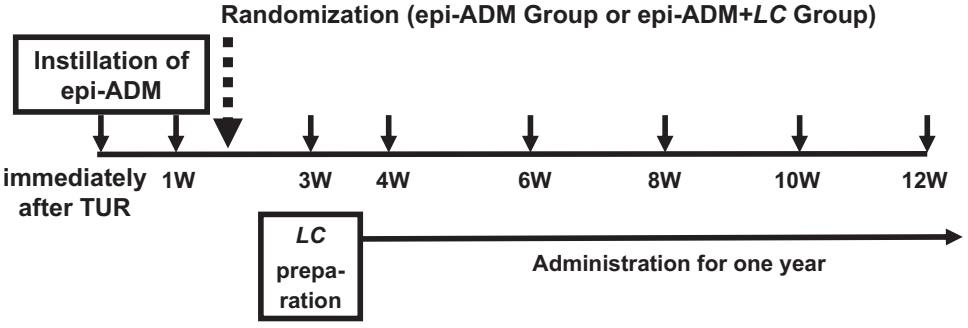


FIG. 1. Treatment schedule of EPI-ADM and EPI-ADM plus LC groups. In EPI-ADM group 30 mg EPI-ADM/30 ml saline were given immediately after (within 2 hours), and 1, 3, 4, 6, 8, 10 and 12 weeks (*W*) after TUR. In EPI-ADM plus LC group same intravesical instillation schedule was used as in EPI-ADM group plus oral administration of 3 gm LC preparation per day, which was begun within 2 weeks after randomization and continued for 1 year.