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SESSION III

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Prospective randomized study of prophylaxis of superficial bladder cancer with epirubicin: the role of a central pathology laboratory

Abstract The preliminary results of a multi-institutional prospective randomized study of the prophylaxis of superficial bladder cancer using epirubicin (protocol NUORG SBT-003) are reported. The subjects were 129 patients with untreated superficial bladder cancer (≦T1b, ≦G2) who were randomized into 2 groups: a transurethral resection (TUR)-alone group (63 patients) and a TUR + intravesical epirubicin (20 mg/40 ml, 30 times/2 years) group (66 patients). The nonrecurrence rate observed in the epirubicin group was significantly higher than that seen in the control group. To unify the pathological diagnosis, a central pathology laboratory (CPL) was set up for extramural review. The correspondence of the pathological diagnosis of TUR-Bt specimens between the CPL and the local pathology laboratory (LPL) was 70.5% in grading and 51.9% in staging. There was a tendency for overdiagnosis by the LPL for both the grade and the stage of tumors. However, differing interpretations by pathologists seem to exert little influence on the nonrecurrence rate at interim analysis. Further observation will be necessary to clarify the prophylactic efficacy of low-dose, long-term periodic intravesical epirubicin instillation and the influence of the disagreement in pathological findings between the CPL and the LPL on the analysis of the results.

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Key words Superficial bladder cancer · Prophylaxis · Epirubicin · Pathological review

Introduction

Superficial bladder cancer of grade 1–2 and stage ≦pT1b seems to have a good prognosis, but 70% of patients will experience recurrence. In many reports concerning effective intravesical prophylactic agents, epirubicin has been shown to be effective and to cause a lower incidence of side effects. A relatively low dose of epirubicin (20 mg/40 ml physiological saline) in long-term periodic instillation (30 instillations/2 years) was assessed in a multi-institutional prospective randomized study conducted by Nara Medical University (protocol NUORG SBT-003).

As prognostic factors of superficial bladder cancer, the pathological grade and stage are recognized as being the most important. For unified pathological diagnosis, the central pathology laboratory (CPL) functioned as the extramural review. We report the preliminary results obtained on the efficacy of intravesical epirubicin as prophylaxis following transurethral resection of bladder tumors (TUR-Bt), mainly focusing on the correspondence in the pathological diagnosis between the CPL and local pathological laboratories (LPL).

Patients and methods

From June 1, 1991, to August 31, 1993, a total of 129 patients were enrolled in this study. They were younger than 75 years, were diagnosed as having untreated superficial bladder cancer (≦T1b, ≦G2), and had undergone TUR-Bt at Nara Medical University or 1 of its 21 affiliated hospitals (Table 1).

After confirmation of the complete surgical resection of bladder tumor and, hence, their eligibility, all patients granted informed consent and were randomized into two groups by a telephone-registration system. Thus, 66 patients were randomly assigned to a group receiving periodic intravesical instillation of epirubicin (E group) and 63 patients were placed in a group that received TUR-Bt alone as

Table 1 Institutions participating in study SBT-003

Institution	Director or chief
Nara Medical University Hospital	E. Okajima
National Nara Hospital	K. Tsumatani
Nara Prefecture Nara Hospital	Y. Kaneko
Nara Prefecture Mimuro Hospital	S. Ohara
Nara Prefecture Gojo Hospital	S. Tabata
Yamato-Takada Municipal Hospital	K. Yoshida
Haibara General Hospital	K. Sasaki
Saiseikai Nara Hospital	H. Aoyama
Saiseikai Chuwa Hospital	H. Watanabe
Nara Rehabilitation Center	O. Natsume
Takai Hospital	N. Morita
Takanohara General Hospital	H. Matsuki
Hirao Hospital	K. Hirao
Hoshigaoka Kohsei-Nenkin Hospital	K. Yamada
Nissei Hospital	T. Hiramatsu
Kaisei Hospital	S. Ikuma
Tane General Hospital	Y. Hayashi
Bobath Memorial Hospital	T. Shiomi
Ishinkai Yao Hospital	A. Iwai
Asakayama General Hospital	K. Babaya
Matsusaka Central Hospital	Y. Maruyama
Okanami General Hospital	M. Yoshikawa

the control (C group). The patients' age and sex as well as the clinical stage, number, and size of the tumors did not differ significantly between the two groups.

All the hematoxylin and eosin (H&E)-stained slides of TUR-Bt specimens were sent to the CPL and reviewed by a single pathologist (S. F.) to unify the pathological diagnosis for comparison with the diagnosis made by the LPL. Patients diagnosed as having tumors of grade 3 or above stage pT2 by the CPL were excluded from the study. Five C-group cases and two E-group cases were regarded as ineligible by the LPL, whereas six C-group cases and three E-group cases were regarded as ineligible by the CPL (Table 2).

All patients were to be followed for a minimum of 5 years by periodic cystoscopy and urinary cytology, which were scheduled to be performed every 3 months in the first 3 years, then every 6 months for

Table 2 Characteristics of the superficial bladder cancer patients entered in protocol NUORG SBT-003[a]

Characteristics	TUR alone		EPI-ADM	
Number of cases	63		66	
Age (years)	58.9 ± 9.6		58.4 ± 10.9	
M:F	49:14		54:12	
Clinical stage:				
Ta	22		17	
T1	41		49	
Number of tumors:				
1	47		47	
2–4	16		13	
≥5	0		6	
Tumor size (cm):				
<1	22		18	
1≦∅<3	37		41	
≥3	4		7	
	LPL	CPL	LPL	CPL
Ineligible by	5	6	2	3
Number of eligible cases (CPL)	58	57	64	63

[a] Nara Medical University, August 1993

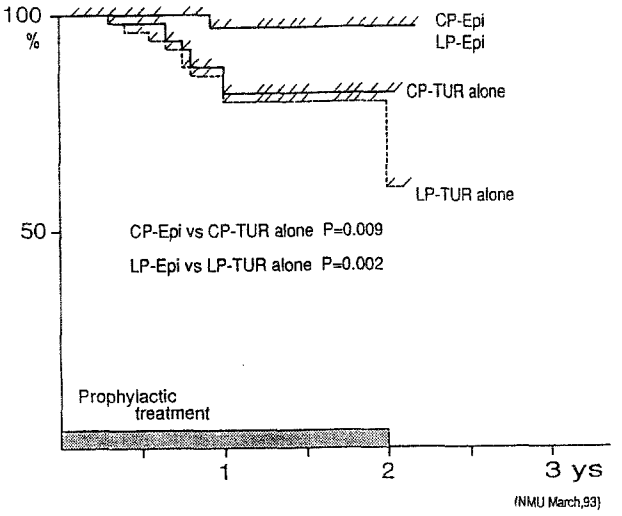

Fig. 1 Nonrecurrence rates determined according to the prophylactic treatment received following TUR-Bt (protocol NUORG SBT-003)

2 years, and yearly thereafter. The treatment was not to alter until a third recurrence. However, patients with progressive disease (grade 3 or above stage pT2) at the time of recurrence were allowed to receive other appropriate treatment.

Results

To date, recurrences have been observed in only 1 of 66 patients (1.5%) in the E group as compared with 6 of 63 patients (9.5%) in the C group. The recurrence was a one-time event in each case. The mean observation period was 13.0 ± 7.7 months in the E group and 12.0 ± 7.0 months in the C group. The nonrecurrence rates produced by intravesical instillation in the E group were significantly higher than those recorded for the C group as based on the data from the CPL as well as the LPL. Moreover, there was no significant difference in the nonrecurrence rates obtained in the E group by the CPL versus the LPL (Fig. 1).

The pathological grading of 129 cases by the LPL showed 2 cases of G0, 23 cases of G1, 101 cases of G2, and 3 cases of G3. The CPL grading according to the highest grade showed 1 case of G0, 38 cases of G1, 83 cases of G2, 5 cases of G3, and 2 cases of Gx. Correspondence in the highest grade determined by the CPL and LPL was seen for 91 of the 129 cases (70.5%), whereas overgrading by the LPL occurred in 24 cases (18.6%) and undergrading was seen in 12 cases (9.3%; Table 3). The CPL grading according to the predominant grade showed G0 in 1 case, G1 in 59 cases, G2 in 66 cases, G3 in 1 case, and Gx in 2 cases. Correspondence in the predominant grade determined by the CPL and LPL was seen for 82 of the 129 cases (63.6%), whereas overgrading by the LPL occurred in 41 cases (31.7%) and undergrading was seen in 4 cases (3.1%; Table 4).

Table 3 Histopathological grading according to the highest grade: LPL versus CPL[a]

CPL grade	LPL grade				Total
	G0	G1	G2	G3	
G0	1	0	0	0	1
G1	1	15	22	0	38
G2	0	7	74	2	83
G3	0	1	3	1	5
Gx	0	0	2	0	2
Total	2	23	101	3	129

[a] Grading correspondence, 91/129 (70.5%); overgrading by LPL, 24/129 (19%); Ungergrading by LPL, 12/129 (9%); Nara Medical University, August 1993

Table 4 Histopathological grading: LPL versus CPL[a]

CPL grade (predominant)	LPL grade				Total
	G0	G1	G2	G3	
G0	1	0	0	0	1
G1	1	20	38	0	59
G2	0	2	61	3	66
G3	0	1	0	0	1
Gx	0	0	2	0	2
Total	2	23	101	3	129

[a] Grading correspondence, 82/129 (63.6%); overgrading by LPL, 41/129 (32%); undergrading by LPL, 4/129 (3%); Nara Medical University, March 1993

Table 5 Histopathological staging: LPL versus CPL[a]

CPL stage	LPL stage				Total
	Ta	T1	Tis	Tx	
Ta	43	52	1	2	98
T1	3	24	0	0	27
Tis	1	0	0	0	1
Tx	3	0	0	0	3
Total	50	76	1	2	129

[a] Staging correspondence; 67/129 (51.9%); overstaging by LPL, 53/129 (43%); understaging by LPL, 4/129 (3.1%); Nara Medical University, August 1993

Pathological staging by the LPL showed Ta in 50 cases, T1 in 76 cases, Tis in 1 case, and Tx in 2 cases. Pathological staging by the CPL showed Ta in 98 cases, T1 in 27 cases, Tis in 1 case, and Tx in 3 cases. Correspondence in the stage was seen in 67 of the 129 cases (51.9%), whereas overstaging by the LPL occurred in 53 cases (41.1%) and understaging was seen in 4 cases (3.1%; Table 5). Thus, the pathological diagnosis of TUR-Bt specimens by the LPL seems to have a tendency to overread in both grade and stage.

Since disease grade and stage are the most valuable prognostic factors, the nonrecurrence rates were evaluated on the basis of both the LPL and the CPL data to determine the influence of the different interpretations by different pathologists on the statistical analysis of the prophylactic efficacy. In the determination of nonrecurrence rates according to grade, the E group was higher than the C group in both the G1 and G2 categories. The nonrecurrence rates determined according to pathological grade by the LPL and CPL did not differ significantly (Fig. 2). In the determination of nonrecurrence rates according to stage, the E group was higher than the C group for both Ta and T1 categories. The nonrecurrence rates determined according to pathological stage by the LPL and CPL were not significantly different (Fig. 3). However, the prophylactic effect of epirubicin was more clearly demonstrated in the data of the CPL than in those of the LPL.

Thus, different interpretations by pathologists seem to exert no influence on the evaluation of the prophylactic effect when all cases are evaluated. However, the influence of the different interpretations by pathologists on the statistical analysis and the role of the CPL in this prospective randomized trial on prophylaxis of the recurrence of superficial bladder cancer should be clarified in the long-term follow-up.

Discussion

There have been many reports concerning the anticancer agents that are effective in intravesical chemotherapy as therapeutic and prophylactic agents. Among the many new anticancer agents, Adriamycin (ADM) has been shown to be effective both as a therapeutic agent and as a prophylactic agent [6], but local and systemic side effects produced by intravesical instillation of ADM have been reported, despite its having a relatively large molecular weight and being poorly absorbed through the bladder well [3].

Epirubicin has been shown to be as effective as its parent compound (ADM) for therapeutic use, and it causes a lower incidence of side effects [2, 7, 10]. A high dose of intravesical epirubicin (50 mg/50 ml) has been used as therapeutically and has produced a favorable overall response rate of 59%, but the duration of response was short. However, a high incidence of side effects such as chemical cystitis (35%) and cardiovascular disorders (4/37; 11%) were reported [4]. For prophylactic treatment with epirubicin, we selected a relatively low dose of epirubicin (20 mg in 40 ml physiological saline) and long-term periodic instillation (30 instillations/2 years) in the present study.

To date, we have observed only one recurrent case in the E group as compared with six cases in the C group. The nonrecurrence rates produced by intravesical instillation in the E group were significantly higher than those recorded for the C group. Moderate chemical cystitis and general fatigue were observed in only 2/63 and 1/63 treated patients, respectively. The remaining patients continued the instillation on schedule without showing any side effects. However, most of the patients in the E group are continuing the intravesical instillation, and it is thus too early to conclude the prophylactic efficacy of intravesical epirubicin in this report.

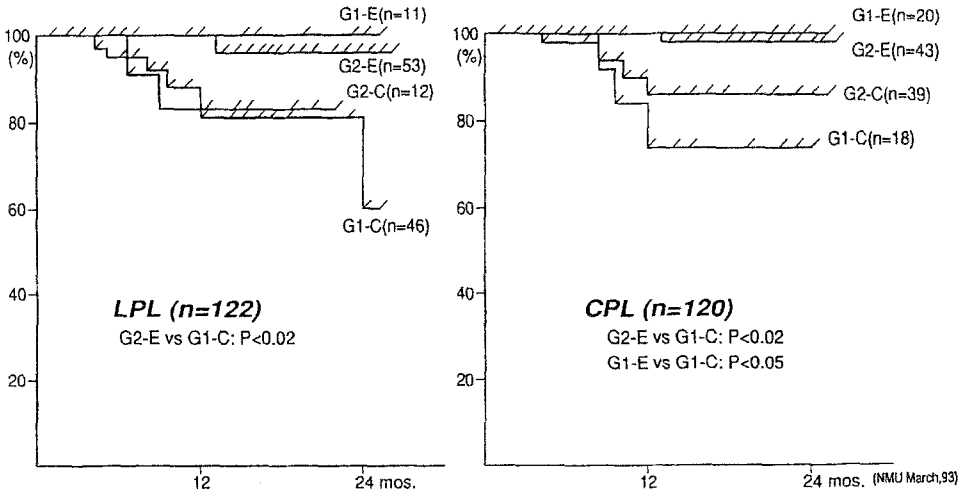

Fig. 2 Nonrecurrence rates determined according to pathological grade by the Kaplan-Meier method

The different interpretations made by the LPL and the CPL were unexpectedly frequent. However, disagreement in the pathological findings between the pathologists of local institutions and the pathologist of a central review laboratory are well reported [1, 5, 11]. Even when the same pathologist performs a reexamination after an interval, the results may differ from those obtained in the first examination [9]. All the pathological diagnoses were based on the General Rule for Clinical and Pathological Studies on Bladder Cancer established jointly by the Japanese Urological Association and the Japanese Pathological Society in 1980, but the details of the diagnostic criteria may differ individually among pathologists.

In this study, the nonrecurrence rate determined according to treatment, stage, and grade was not seriously affected by the paradoxical results obtained by the LPL versus the CPL. Parmar et al. [8] reported that the disease grade was an important prognostic factor when assessed by the reference pathologist, but no trend was found in relation to the tumor grade when the data were assessed by local pathologists for the evaluation of prognostic factors in two large randomized British Medical Research Council studies [8]. Considering these differing interpretations by pathologists, extramural review of pathological findings by a CPL is desirable to unify the pathological findings, one of the most important prognostic factors of superficial bladder cancer, in large-scale multi-institutional prospective randomized trials.

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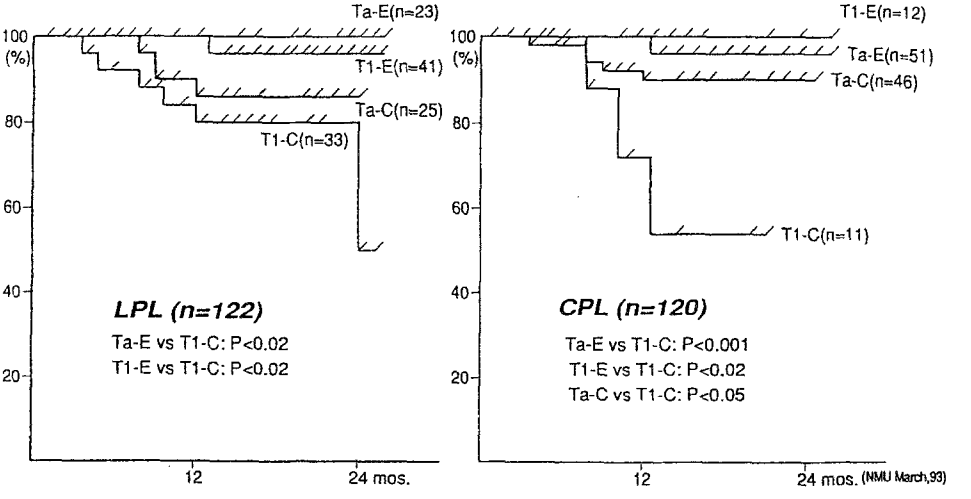

Fig. 3 Nonrecurrence rates determined according to pathological stage by the Kaplan-Meier method

Long-term follow-up in superficial transitional cell carcinoma of the bladder: prognostic factors for time to first recurrence, recurrence rate, and survival. Final results of an EORTC randomized trial comparing doxorubicin hydrochloride, ethoglucid, and transurethral resection alone. In: Murphy GP, Khoury S (eds) Therapeutic progress in urogenital cancers. Alan R. Liss, New York, p 481

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