15-Year Survival Rates after Transurethral Resection and Radiochemotherapy or Radiation in Bladder Cancer Treatment

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Abstract. *Objective: To evaluate 15-year experience with patients treated with transurethral resection (TUR) of a bladder tumor (TURBT) followed by radiochemotherapy (RCT) or radiation (RT) and to describe the association of different parameters with clinical outcome. Patients and Methods: Bladder cancer patients (473) who underwent TURBT and RCT or RT with curative intent between 1982 and 2007 in our clinic were evaluated. The clinical course, operative and pathological characteristics and the long-term clinical outcome were assessed. Results: Complete remission (CR) was achieved in 70.4% of the patients. The 5-, 10- and 15-year overall survival rates were 49%, 30% and 19%, respectively. Long-term results were significantly affected by pT stage, lymphatic vessel invasion, residual tumor status, lymph node metastasis, kind of therapy (RCT vs. RT), and the response as confirmed by restaging TUR after RCT/RT. Conclusion: Organ-preservation therapy in patients with bladder cancer is a valid option compared to radical cystectomy in selected patients, ideally with early-stage bladder cancer, in whom a complete transurethral resection of the tumor can be accomplished and radiochemotherapy is superior to radiation for favorable long-term outcome.*

Bladder cancer is the ninth most common malignant tumor worldwide (~357,000 cases/year), with the highest rates of ~30/100,000 people in southern/western Europe and North America (1). Although the majority of patients present with superficial bladder tumors, 20-30% either present with invasive disease or develop it.

During the past 35 years, radical cystectomy and pelvic lymph node dissection have emerged as standard therapy for invasive bladder cancer (2). Alternatively, transurethral resection (TUR) of the bladder tumor (TURBT) combined with radiochemotherapy (RCT) has been reported to be as effective as cystectomy in selected patients (3-5).

The ment of TURBT and RCT as an alternative therapy option, however, is restricted since available data involving meaningful numbers of patients and observation periods are limited. Most of the published series have included fewer than 100 patients and the success of the combined treatment has been judged on the basis of, at most, a 5-year follow-up. Here, 15-year, long-term experience with 473 patients treated with TURBT and RCT or radiation therapy (RT) for transitional cell cancer (TCC) of the bladder is reported.

Patients and Methods

Patient population. A computerized database was established containing detailed and comprehensive clinical and pathological information about patients who underwent TURBT and RCT or RT between 1982 and 2007 at our institution. Four hundred and seventy-three consecutive patients, 366 men and 107 women, with a mean age of 65.3 years (range: 28-91 years) at the time of treatment were evaluated. The median follow-up was 71.5 months, with a range from 1.9 to 306 months. The status at the time of data collection was: alive without tumor, n=104 (22.0%); alive with tumor or unknown tumor status, n=10 (2.1%); died without tumor, n=105 (22.2%); died because of tumor, n=186 (39.2%); and died with unknown tumor status, n=68 (14.4%). An observation period of 5 to 10 years was evaluable for 123 patients; of 10 to 15 years for 63 patients, and 41 patients were observed for more than 15 years.

Treatment protocol. Treatment began with TURBT aimed at complete resection of the tumor mass, if feasible. Putative residual tumor was assessed histologically by biopsies from all the resection

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margins, with pR0 indicating microscopically complete TURBT and pR1 a microscopically residual tumor. The macroscopically residual tumor in cases of huge tumor masses was categorized as cR2. The T category was assessed according to the TNM classification of 1987 (International Union Against Cancer) (6), thus grouping all subepithelial tissue-invading tumors into stage pT1, all superficial muscle-invasive tumors into stage pT2, all deep muscle-invasive tumors into stage pT3, and any tumor with evidence of invasion of surrounding organs into stage pT4. Since 1997, tumor staging has been modified according to the 1997 TNM classification by the American Joint Committee on Cancer (7). For the purpose of the present analysis, all stages were redefined according to the 1987 TNM system, and pT2 and pT3 were merged into one group (pT2/pT3=muscle-invasive) to make comparisons with other published series possible. In all the cases, clinical staging was completed by chest X-ray and computed tomography of the abdomen and pelvis. No patient had any evidence of distant metastasis (cM0) before starting the treatment.

RT was initiated 4 to 6 weeks after TURBT using 6- to 10-MV photons and a four-field box technique with individually shaped portals and daily fractions of 1.8 to 2 Gy on 5 consecutive days. A median dose of 53.9 Gy (range 23.4-69.4 Gy) was applied to the bladder and pelvic nodes. Chemotherapy was given simultaneously for 5 consecutive days during the first and fifth weeks of RT. A total of 99.4% of the patients received a platinum-based chemotherapy: 143 cisplatin, 97 carboplatin, 67 cisplatin/5-FU, 6 carboplatin/5-FU, 9 cisplatin/carboplatin, 4 cisplatin/carboplatin/5-FU, 2 5-FU, and 3 cisplatin/gemcitabine. RCT was conducted in 331 patients (70%) and 142 patients (30%) received radiation as a single therapy. There were no tumor-specific exclusion criteria for RCT. The reasons for RT-only therapy were age of patient, high comorbidity and performance status.

Six weeks after the completion of RT/RCT, treatment response was evaluated by restaging TUR. Patients with persistent tumor were considered non-responder (NR), and tumor-free patients were categorized as complete responder (CR).

In 125 NRs, additional operative treatment was carried out. Out of these, 63 received salvage cystectomy and 62 had re-TURBTs (one or more) with or without topical chemoinstillation, accounting for 13.3% and 13.1% of all the patients assessed, respectively. Table I summarizes the patient characteristics.

Statistics. Survival functions were estimated according to the Kaplan-Meier method. The observed survival time of a patient ranged from the date of diagnosis to either the patient's death or the time of censoring. A patient was censored if still alive at the end of the observation time. The estimated survival functions were plotted as Kaplan-Meier curves. Log-rank tests were performed to test whether two or more functions were identical. Because survival may depend on patient age at the time of diagnosis, the Mantel-Haenszel version of the log-rank test stratified by age was used. Therefore, the patients were divided into three almost equal age groups (up to 60 years, 61-70 years, and 71 years and older). All the hypothesis tests were two-sided. The *p*-values of the main analysis were adjusted using the Bonferroni-Holm method for multiple testing. In addition, a subgroup analysis including the TURBT and RCT patients was performed to compare clinical outcome with the total cohort (TURBT and RCT or RT). A *p*-value less than 0.05 was considered to indicate statistical significance. All the statistical analyses were carried out using the R system for statistical computing (version 2.8.0; R Development Core Team, Vienna, Austria; 2008).

Table I. *Patient characteristics: staging parameters after TURBT and before RCT or RT.*

Variable		No. of patients	%
pT	1	110	23.3
	2/3	328	69.3
	4	34	7.2
Acc. Cis	Cis	92	19.5
	No Cis	381	80.5
Grade	I	17	3.6
	II	190	40.2
	III	266	56.2
cN	0	414	87.5
	+	29	6.1
	Unclear status	30	6.3
pL	pL0	284	60.1
	pL1	189	39.9
Focality	Uni	282	59.6
	Multi	151	31.9
	Not reported	40	8.5
R	0	142	30.0
	1	152	32.1
	2	160	33.8
	Not reported	19	4.1

Results

The median survival for all 473 patients treated with TURBT and RCT or RT was 57.5 months with the 5-, 10- and 15-year overall survival rates (YSRs) being 49%, 30% and 19%, respectively. The most significant predictors of outcome in the statistical analysis were tumor infiltration depth, invasion of lymphatic vessels, lymph node metastasis, achievement of pR0 status after TURBT, and complete remission as confirmed by restaging TUR (Tables II and III). No effect on outcome was seen for associated carcinoma *in situ*, tumor grade, or focality of the tumor in the bladder.

pT Stage. The infiltration depth of the TCC was highly statistically significant ($p<0.00001$) for the long-term outcome of the combined treatment (Figure 1a). The 5-, 10- and 15-YSRs for pT1 tumors were 71%, 48% and 30%; for pT2/T3 tumors, they were 45%, 26% and 16%, and for pT4 tumors, they were 15%, 7% and 0%, respectively.

Lymph node metastasis. The clinical presence of lymph node metastasis (cN1–cN3) correlated significantly ($p<0.001$) with a lower life expectancy. The 5-, 10- and 15-YSRs for this group were 14%, 10% and 10%, respectively, compared to patients with cN0, with 5-, 10- and 15-YSRs of 52%, 32% and 19%, respectively (Figure 1b).

Lymphatic vessel invasion. The detection of lymphatic vessel invasion in the resected tissue samples was a highly

Table II. *Effect of characteristics on survival outcome according to Mantel-Haenszel log-rank test stratified by age (raw and adjusted p-values); (total patient group: n=473).*

Variable	*p*-Value (raw)	*p*-Value (adjusted)
pT	<0.00001	<0.00001
Acc. Cis	0.77	1.00
Grade	0.76	1.00
cN	<0.0001	<0.001
pL	<0.00001	<0.0001
Focality	0.64	1.00
Response	<0.00001	<0.00001
Resection	<0.00001	<0.00001
Therapy	<0.001	<0.001

significant parameter ($p<0.0001$) for long-term outcome after 5, 10 and 15 years following combined treatment (Figure 1c). Patients with pL0 had a median survival of 74 months, while those with pL1 had a median survival of 26 months.

Response status. CR as detected by restaging TUR was determined for 333 patients (70.4%). NR for 126 patients (26.2%), and no information about the remission status could be obtained for the remaining 14 patients. The achievement of CR was significantly correlated ($p<0.00001$) with long-term outcome with 5-, 10- and 15-YSRs of 60%, 38% and 23%, respectively, compared to NRs with 23%, 12% and 9%, respectively (Figure 1d).

Residual tumor status. A tumor-free resection (R0) was a highly significant parameter ($p<0.00001$) for long-term outcome with survival rates of 70%, 46% and 35% after 5, 10 and 15 years, respectively, compared to patients with R1 or R2 (Figure 1e). In the case of residual tumor resection, R1 seemed to be more favorable, with better survival rates of 47%, 30% and 16%, respectively, than R2 with 33%, 16% and 7%, respectively.

Radiation vs. radiochemotherapy. RCT following TURBT was a significant parameter ($p<0.001$) for survival (Figure 1f). Patients receiving TURBT and RCT showed a median survival of 70 months; those with RT-only treatment after TURBT had a median survival of 28.5 months.

Focusing on the subgroup of 331 patients treated with TURBT and RCT, a median survival of 70 months was found with overall 5-, 10- and 15-YSRs of 54%, 36% and 24%, respectively. As for the whole cohort, the prognosis significantly correlated with pT stage, lymph node metastasis, lymphatic vessel invasion, the achievement of CR and the achievement of R0 resection at the initial TURBT. The results of the Mantel-Haenszel log-rank test, stratified by age, for patients with TURBT and RCT were highly significant for pT, response and R ($p<0.00001$), very significant for cN ($p<0.0001$), and significant for pL ($p<0.001$). Table IV gives the results of the subgroup analysis.

Table III. *Estimated median survival time in months and 5-, 10- and 15-year survival rates (YSRs) according to the Kaplan-Meier method (95% confidence intervals in brackets) for 473 patients following TURBT and RCT or RT.*

Variable		Median survival (months)	5-YSR (%)	10-YSR (%)	15-YSR (%)
pT	T1	119 (89-166)	71 (62-80)	48 (39-59)	30 (21-44)
	T2/3	44 (32-61)	45 (40-51)	26 (22-32)	16 (12-22)
	T4	17 (11-22)	15 (7-33)	7 (2-26)	0
Acc. Cis	Cis	62 (37-93)	52 (43-63)	29 (21-41)	15 (8-28)
	No Cis	58 (40-66)	48 (43-53)	30 (26-36)	19 (15-24)
Grade	II	58 (42-71)	49 (42-57)	29 (23-37)	17 (11-24)
	III	49 (34-68)	47 (41-54)	29 (24-36)	21 (16-28)
cN	0	63 (49-75)	52 (47-57)	32 (28-38)	19 (15-25)
	+	20 (16-26)	14 (6-34)	10 (4-30)	10 (4-30)
pL	1	26 (19-38)	37 (31-45)	22 (16-29)	13 (9-20)
	0	74 (62-96)	56 (51-63)	36 (30-42)	21 (16-28)
Focality	Multi	62 (37-85)	51 (44-60)	32 (25-41)	20 (13-29)
	Uni	59 (46-73)	49 (44-55)	29 (24-36)	18 (13-24)
Response	CR	80 (70-98)	60 (55-66)	38 (33-44)	23 (18-29)
	NR	17 (14-21)	23 (16-31)	12 (8-20)	9 (5-17)
Resection	R0	116 (92-168)	70 (63-78)	46 (37-56)	35 (26-47)
	R1	54 (36-70)	47 (39-55)	30 (23-38)	16 (10-25)
	R2	19 (16-28)	33 (26-41)	16 (11-23)	7 (4-13)
Therapy	RT	29 (23-42)	36 (29-45)	17 (12-25)	8 (4-14)
	RCT	70 (58-85)	54 (49-60)	36 (31-43)	24 (19-30)

CR: Complete responder; NR: non-responder; RT: radiation therapy; RCT: radiochemotherapy.

Table IV. *Estimated median survival time in months and 5-, 10- and 15-year survival rates (YSRs) according to the Kaplan-Meier method (95% confidence intervals in brackets) for 331 patients treated with TURBT and RCT.*

Variable		Median survival (months)	5-YSR (%)	10-YSR (%)	15-YSR (%)
pT	1	121 (104-166)	73 (64-83)	51 (41-64)	34 (23-50)
	2/3	60 (42-75)	50 (44-57)	32 (26-39)	22 (17-30)
	4	18 (10 - 50)	16 (6-45)	11 (3-39)	0
cN	0	77 (66-98)	58 (52-64)	39 (33-46)	27 (21-34)
	+	20 (12-54)	14 (5-41)	10 (3-36)	0
pL	1	27 (23-67)	43 (35-53)	28 (21-37)	17 (11-26)
	0	91 (68-119)	60 (54-67)	40 (34-48)	28 (21-37)
Response	CR	93 (77-121)	64 (58-70)	43 (37-50)	27 (21-35)
	NR	17 (14-24)	25 (17-37)	15 (8-26)	13 (7-24)
Resection	R0	142 (93-168)	72 (64-81)	50 (41-62)	45 (35-59)
	R1	61 (42 - 85)	52 (43-61)	35 (28-46)	22 (14-32)
	R2	26 (17-50)	37 (29 - 48)	19 (12-29)	8 (4-18)

CR: Complete responder; NR: non-responder.

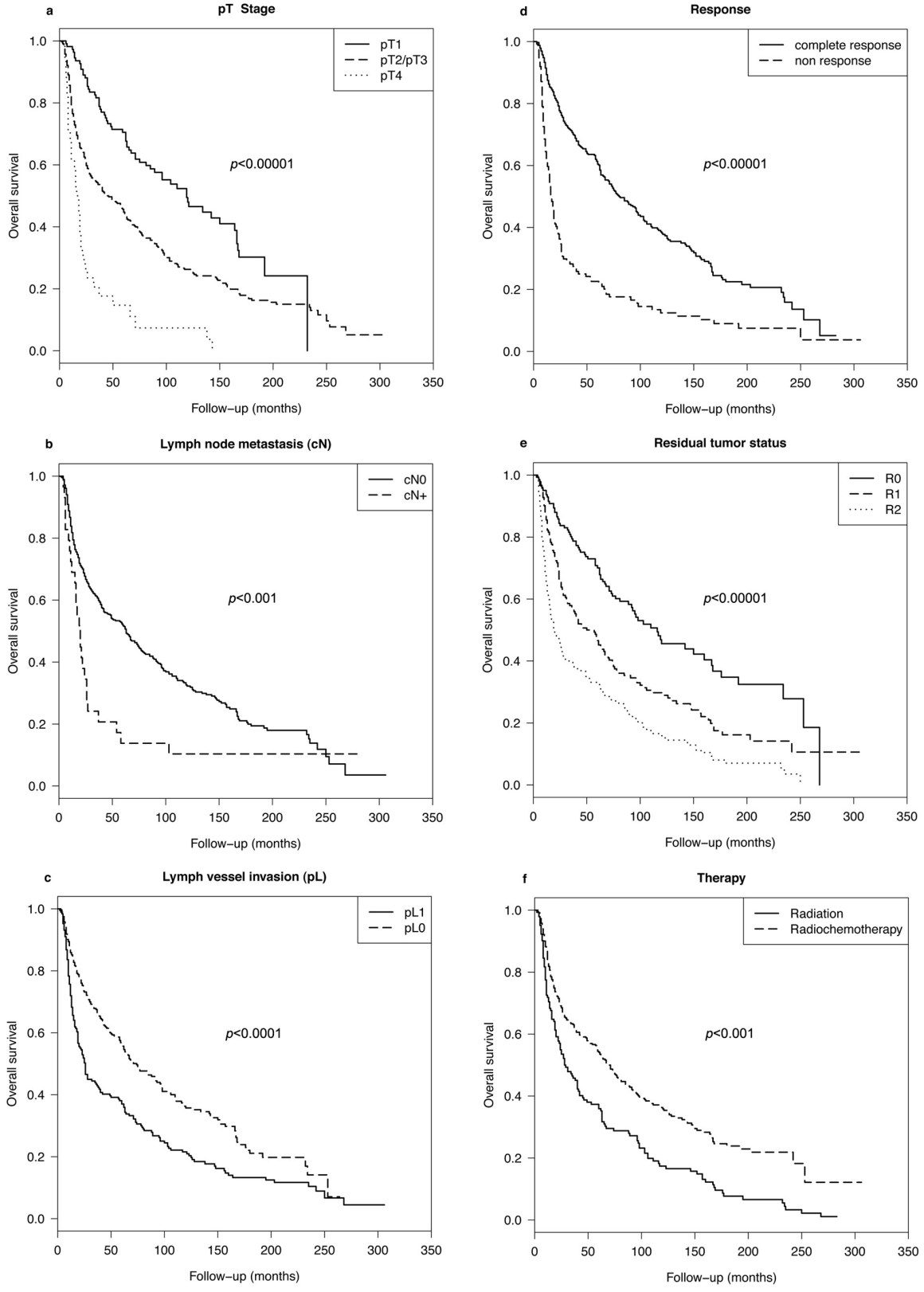

Figure 1. *Kaplan-Meier estimates of overall survival as related to different clinical parameters in patients with bladder cancer after TURBT and RCT or RT. P-values were calculated using the Bonferroni-Holm method for multiple testing.*

Table V. *Comparison of studies using two different curative therapy options (TURBT+RCT versus radical cystectomy) and the long-term outcome (5-, 10- and 15-year survival rates, YSRs).*

	Therapy	Stage	No of pts	5-YSR (%)	10-YSR (%)	15-YSR (%)
Present series	TURBT + RCT	T1–T4	331	54	36	24
Retz *et al*. (15)	TURBT + RCT	T2–T4	53	23	8	-
Danesie *et al*. (4)	TURBT + RCT	T2–T4a	77	58	-	-
Gogna *et al*. (12)	TURBT + RCT	T2–T4	113	50	-	-
Kragelj *et al*. (16)	TURBT + RCT	T1–T4	84	-	25	-
Stein *et al*. (2)	Rad. cystectomy	T0–T4	1054	60	43	-
Hautmann *et al*. (17)	Rad. cystectomy	Ta–T4	788	58	45	-
Yossepowitch *et al*. (18)	Rad. cystectomy	T0–T4	483	61	-	-
Madersbacher *et al*. (19)	Rad. cystectomy	Ta–T4	507	59	37	-

Discussion

To date, only a few studies on a combined treatment modality with TURBT and RCT or RT for bladder preservation in patients with invasive bladder cancer have been published and the present cohort, including a total of 473 patients, to our knowledge, represents the largest series of bladder cancer patients from a single institution with an organ-preserving treatment approach evaluated.

CR of the tumor was achieved in more than 70% of the patients and infiltration depth, lymphatic vessel invasion, residual tumor after initial TURBT, lymph node metastasis and the remission status six weeks after cessation of therapy all significantly predicted clinical outcome. Perdona *et al*. (3) also found a significant effect of tumor stage, remission status after completion of radio(chemo)therapy, and treatment modality (RCT *vs*. RT) on long-term survival, with a median follow-up time of 66 months. Danesie *et al*. (4) reported 90% CR in 72 patients, of whom 57% were still alive after an average observation period of 82 months. However, no significant difference in long-term survival was observed for most clinicopathological features except tumor stage (T2 *vs*. T3/4a). The survival of patients with pT2 tumors was also better than those with pT3 tumors in a study by Cobo *et al*. (5).

Thus, the proper selection of patients most likely to benefit from the bladder-preserving approach is warranted. The ideal candidate is a patient with a pT1 tumor that can be completely removed by initial TUR and that shows CR in restaging TUR following RCT or RT.

The optimal treatment regimen and combination of RT and chemotherapy after TURBT remains to be established. In the present cohort, long-term survival after RCT (70 months) proved to be significantly superior to RT (28.5 months). These rather poor survival data for RT following TURBT in the present series are in accordance with what has been reported in the literature (8-11).

The rationale for a combination treatment of radiation with chemotherapy is twofold. Firstly, certain cytotoxic agents may have the potential of sensitizing tumor cells to radiation and inhibiting repopulation during radiotherapy, thus increasing local cure rates. Secondly, since as many as 10% of superficially infiltrating tumors and 50% of muscle-invasive tumors have already developed occult metastases, systemic chemotherapy may help to eradicate them. Although most chemotherapies that have been applied in different studies were platinum-based, the optimal regimen in combination with radiotherapy has yet to be established (12). Newer chemotherapeutic agents such as gemcitabine and the taxanes are potent radiation sensitizers and have shown promising response rates and an acceptable toxicity (13, 14).

Although a direct comparison of the bladder-sparing approach with reported cystectomy series is limited by differences in the patient characteristics, the bladder-sparing approach seems to yield slightly lower 5- and 10-YSRs even in those patients in the present series, who had received TURBT and RCT. Considering local tumor stage, the benefit of cystectomy seems to become more pronounced in more advanced disease. Whereas the 5- and 10-YSRs for the T1 tumors in the present RCT series were comparable to the cystectomy series reported by Stein *et al*. (2), the survival rates for the T2/3 tumors were slightly inferior (50% and 32%, respectively *versus* 58%-72% and 39%-56%, in the Stein *et al*. study) and for the T4 tumors (16% and 11%, respectively, compared to 33-38% and 22%) were considerable lower. The N0 lymph node status was associated with 5- and 10-YSRs of 58% and 39%, respectively, while cN+ with 14% and 10%, respectively in the present series, and these values were again lower than those of the cystectomy series of Stein *et al*. (2) (pN0 69% and 49%, respectively, and pN+ 31% and 23%). Madersbacher *et al*. (19) identified a 5-YSR of 26% for pN+ patients after radical cystectomy. Although patients with more advanced bladder cancer seem to have an advantage with radical surgery in the long-term course than with the organ-preserving approach, prospective and randomized clinical trials are urgently needed to identify reliable risk

factors that allow for better selection of patients who are to undergo immediate radical cystectomy or conservative therapy. The superiority of radiochemotherapy over radiation for the long-term outcome has to be considered in the decision-making process.

In conclusion, the use of organ-preservation therapy in patients with bladder cancer is a valid option compared to radical cystectomy in selected patients, ideally those with early-stage bladder cancer, in whom complete transurethral resection of the tumor can be achieved.

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