ANTICANCER RESEARCH *25*: 1623-1628 (2005)

Radiochemotherapy after Transurethral Resection is an Effective Treatment Method in T1G3 Bladder Cancer

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Abstract. *Aim: Conservative therapy using deep transurethral resection (TUR) followed by radiochemotherapy is a novel treatment strategy in stage TI grade 3 (T1G3) transitional cell carcinoma (TCC) of the bladder. The aim of this study was to present our long-term results of radiochemotherapy in T1G3 TCC patients. Materials and Methods: A total of 64 patients with T1G3 TCC of the bladder underwent a TUR and a subsequent radiochemotherapy protocol at our institution. Following TUR, a median dose of 55.8 (range; 45-69.4) Gy radiation therapy was applied to the bladder, and simultaneous chemotherapy was initiated using cisplatin, carboplatin and\or 5-fluorouracil. After completion of the protocol, response was evaluated by repeat TUR, and check cystoscopies were performed at regular intervals. Median patient age was 66 (range; 30-82) years and median follow-up was 43.2 (range; 6-127) months. Results: Complete response was achieved in 55 (90.2%) patients. Of the complete responders, 7 patients experienced a superficial (Ta, T1) recurrence and 8 patients had progression. In 8 patients with refractory superficial and invasive relapses, a salvage cystectomy was mandated. The overall progression rate was 14%. The overall and disease-free survival rates were 76% and 93%, respectively at 5 years. During follow-up, 4 patients suffered from reduced bladder capacity, and 2 patients underwent cystectomy due to shrinking bladder. Conclusion: Combined multimodality therapy is a safe and curative treatment option for patients with T1G3 TCC of the bladder in the hands of dedicated multimodality teams. Therefore, it is reasonable to justify radiochemotherapy combined with TUR in the first-line treatment of T1G3 tumors.*

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Key Words: Bladder cancer, radiochemotherapy, transurethral resection.

Stage T1 grade 3 (T1G3) transitional cell carcinoma (TCC) are aggressive tumors, that require a close long-term follow-up due to high recurrence and progression rates. When treated with transurethral resection (TUR) alone, 50-80% of patients show recurrences and 33-64% progress (1). Patients with progression are at high risk of dying from bladder cancer, thus they require more aggressive treatment.

The ideal treatment for T1G3 tumors remains controversial and is still developing. The main therapeutic options are TUR of the bladder tumor alone, second resection, intravesical treatment with bacillus Calmette-Guerin (BCG) or chemotherapeutic agents and cystectomy. Currently intravesical BCG is the most commonly recommended treatment and widely used for high risk TCC patients (2-4). On the other hand, some groups recommend immediate cystectomy (5-7).

Combining radiotherapy and simultaneous chemotherapy (RCT) with aggressive TUR is a novel treatment strategy for T1G3 bladder cancers. Recently, TUR of the bladder tumor (TURB), followed by radiotherapy with concurrent radiation-sensitizing cisplatin- based chemotherapy, has been shown to be an effective treatment method in patients with invasive bladder cancer (8, 9). The rationale of using radiotherapy and chemotherapy in high grade T1 bladder cancer arises from the proven efficacy of radiotherapy in prospective series of muscle-invasive TCC, possible eradication of tumor cell deposits in the deep layers of the bladder wall and eradication of occult systemic disease (9, 10). It has been an ongoing policy at our institution to use radiotherapy with or without concurrent chemotherapy after aggressive TUR for invasive and high risk T1 bladder cancers since 1982 (8, 11, 12). The current study provides long-term follow-up data on the RCT treatment of patients with T1G3 TCC of the urinary bladder with emphasis of progression, survival and bladder preservation.

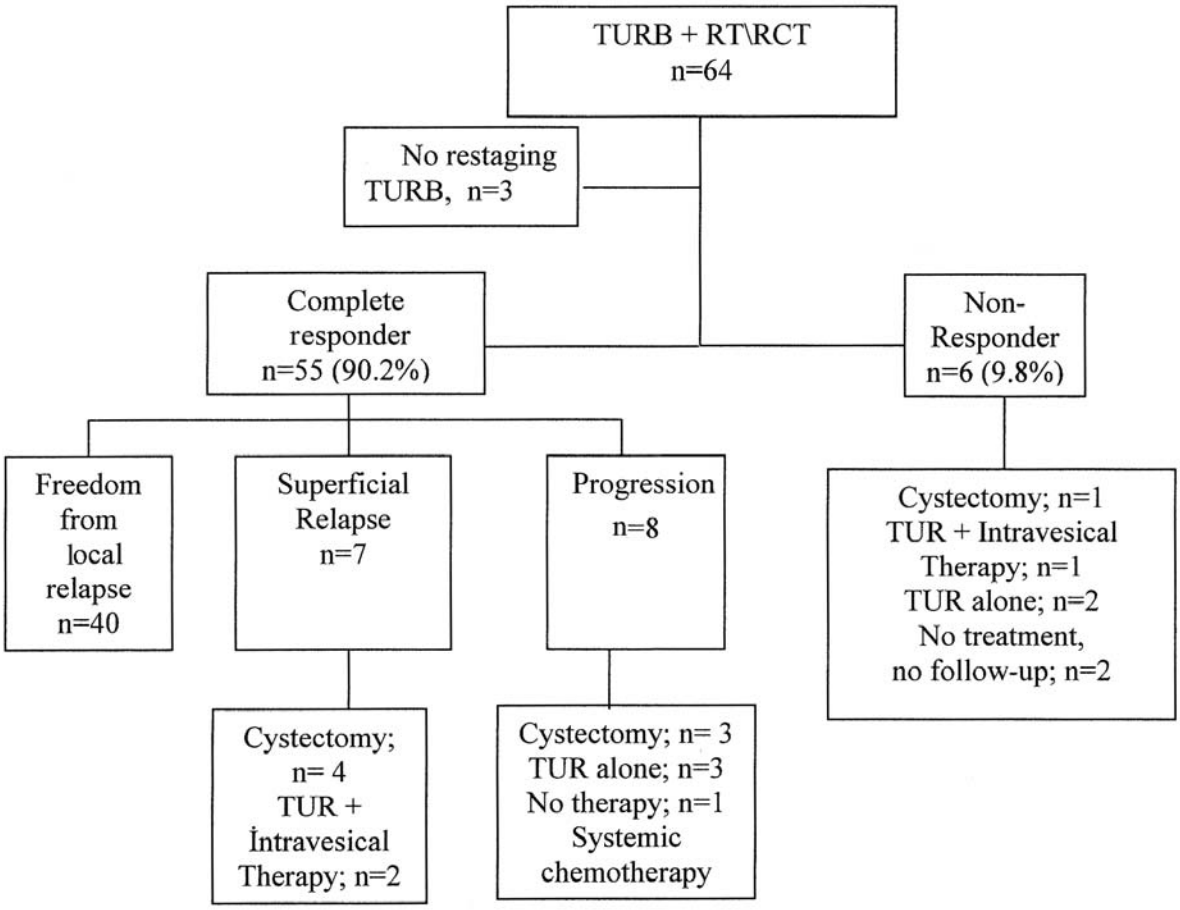

Figure 1. *Initial response, local control and further treatment of patients treated with radiochemotherapy protocol.*

Materials and Methods

Between November 1982 and July 2002, a total of 64 patients with stage T1G3 TCC of the bladder were treated with either radiotherapy alone or with concomitant RCT after initial TUR of the tumor. Median age was 66 (range; 31-82) years. None of the patients had evidence of pelvic lymph node involvement on pretreatment imaging and all patients were free of systemic spread at the time of the onset of the RCT protocol. Multiple TURs prior to RCT or poor general condition with contraindications for radical cystectomy were not considered as exclusion criteria.

Treatment was commenced by cystoscopy and by manual examination under anesthesia with TURB including bladder capacity assessment. First, the tumor was resected into the level of surrounding healthy mucosa, then the deeper fractions were resected as deep as safely possible. Residual tumor assessment was done according to histological examination of biopsies taken from all resection margins: R0 indicated microscopically complete TURB, whereas R1 indicated microscopic tumor residual and R2 macroscopic tumor residual. Histological grade and tumor stage were assessed according to the 1997 version of TNM classification by the American Joint Committee on Cancer (13).

RCT was initiated 4 to 8 weeks after initial TURB using 6- to 10- mV photons and a 4-field box technique with individually shaped portals and daily fractions of 1.8 to 2.0 Gy on 5 consecutive days. A median dose of 55.8 (range, 40 to 61.4) Gy was applied to the bladder; the pelvis was irradiated with a median dose of 50.4 (range, 36 to 54) Gy. Seventeen patients additionally received a median dose of 45 (range 40 to 50.4) Gy to the paraaortic lymph nodes. Twelve patients were treated by radiotherapy alone. Since October 1985, concurrent chemotherapy was given with radiotherapy. Chemotherapy was applied in the 1st and 5th weeks of radiotherapy and consisted of cisplatin (25 mg/m^2/d) in 26 patients, carboplatin (65 mg/m^2/d) in 5 patients with decreased creatinine clearance or congestive heart disease. Since 1993, a combination of cisplatin (20 mg/m^2/d) and 5-fluorouracil (600 mg/m^2/d) was given to 19 patients. One patient received carboplatin and 5-fluorouracil and another one received cisplatin + carboplatin.

Six weeks after completion of the RCT protocol, the response was evaluated by careful cystoscopic examination including bladder capacity assessment and deep TUR of the previous tumor site(s). The absence of endoscopically visible tumor, absence of any microscopic tumor in the biopsy specimen and negative urine cytology were considered as complete response (CR). Those

Table I. *The association between tumor characteristics and complete response rate and progression rate.*

	n	CR (%)	*p*	Progression (%)	*P*
Age					
≤ median	36	91.7	0.13	11.1	0.23
> median	28	78.6		22.2	
Gender					
Female	12	100	0.12	25	0.33
Male	52	82.7		13.7	
Resection status					
R0	35	88.6	0.13	11.8	0.65
R1	21	90.5		19	
R2	7	57.1		28.6	
Unknown	1	100			
CIS					
[+]	27	88.9	0.38	16.1	0.61
[–]	31	80.6		11.5	
Unknown	6				
Multifocality					
Single	33	90.9	0.03	15.2	0.88
Multifocal	30	83.3		17.2	
Unknown	1				
Treatment					
RT	12	66.7	0.03	18.2	0.81
RCT	52	90.4		15.4	
Tumor status					
Primary	42	83.3	0.4	19.5	0.54
Recurrent	22	90.9		9.5	

Table II. *The progression-free survival time of complete responders (n=55) and their relating progression rates.*

	n	Median progression-free survival (months±SE)	*p*	Progression (%)	*p*
Age					
≤ median	33	47.5±4.4	0.04	9.1	0.16
> median	22	22.7±13.8		22.7	
Gender					
Female	12	23.0±0.85	0.3	25	0.24
Male	43	45.2±4.7		11.6	
Resection status					
R0	31	38.3±11.7	0.54	12.9	0.89
R1	19	44.5±1.4		15.8	
R2	4	14.2±24.8		25	
Unknown	1				
CIS					
[+]	25	50.5±5.5	0.77	12	0.95
[-]	24	38.3±1.1		12.5	
Unknown	6				
Multifocality					
Single	30	45.0±4.0	0.29	10	0.29
Multifocal	25	42.9±14.3		20	
Treatment arm					
RT	8	22.7±21.4	0.56	12.5	0.85
RCT	47	44.1±2.5		14.9	
Tumor status					
Primary	36	42.9±4.7	0.16	17.1	0.73
Recurrent	19	50.7±4.2		10.5	

patients were followed up at 3-month intervals for the first 2 years and every 6 months thereafter. During follow-up period, progression was defined as muscular invasion (stage T2 or higher) or metastatic disease. Patients with persistent superficial or invasive tumors following RCT were considered as non-responders. These patients received additional treatment such as TUR plus intravesical therapy or salvage cystectomy.

At the time of analysis, the median follow-up for patients was 43.2 (range; 6-172) months and 20 patients have been followed-up for 5 years or more. Time to progression was considered as the major end-point in calculating statistical analysis. Overall and disease-free survival rates were calculated using the Kaplan-Meier method. Differences were analyzed using the log-rank test and the Chi-square test was used to determine statistical significance between proportions of patient characteristics and end-points. Results were considered statistically significant at a p-value <0.05.

Results

After radiotherapy/RCT, a pathologically complete remission (pCR) was achieved in 55 patients (90.2%) (Figure 1). The association of patient and tumor characteristics with the complete response rates, as well as subsequent progression rates, are shown in Table I. There were statistically significantly fewer complete responders in

Table III. *Toxicity and side-effects related to radiochemotherapy treatment. Chemotherapy-related side-effects are classified according to the World Health Organization (WHO) grading scale.*

Chemotherapy-related	Grade 3 (%)	Grade 4 (%)
Leucopenia	0	0
Thrombocytopenia	4	1
Anemia	0	0
Creatinine elevation	3	0
Nausea\Vomiting	6	0
Diarrhea	4	0

Radiotherapy-related	(%)
Reduced bladder capacity	7
Mild pollakuria	31
Severe pollakuria	2
Mild diarrhea	17
Severe diarrhea	6
Bowel obstruction	0
Temporary dysuria	6

Table IV. *Recurrence (R), progression (P), five-year estimated disease-specific survival (DSS) and median follow-up (months) of patients with T1G3 disease treated with TUR plus BCG and cystectomy.*

Author	n	R (%)	P (%)	DSS (%)	Follow-up
		TUR+BCG Series			
Gohji *et al.* (16)	45	37	4	67	63
Iori *et al.* (17)*	41	24	5	-	40
Baniel *et al.* (18)	75	28	8	-	56
Seretta *et al.* (19)	50	32	12	84	52
Brake *et al.* (20)*	44	27	16	89	28
Hurle *et al.* (3)	51	25	18	86	85
Cookson *et al.* (2)	86	44	19	-	59
Patard *et al.* (21)	50	52	22	80	65
Peyromaure *et al.* (4)*	57	42	22	87	53
Shahin *et al.* (22)	92	70	33	-	63
Zhang *et al.* (23)	23	74	35	88	45
Herr *et al.* (24)	48	-	52	69	180
		Cystectomy series			
Amling *et al.* (5)	166	NA	-	66	120
Freeman *et al.* (6)	182	NA	-	77	120
Stockle *et al.* (7)					
Early	55	NA	-	90	60
Delayed	39	NA	-	61	60
Present series	64	12	14	93	43

* Studies with BCG maintenance.

patients treated with RT alone ($p=0.03$) and in multifocal tumors ($p=0.03$).

Of the 6 non-responder patients, 1 underwent cystectomy and is disease-free after 10 years of follow-up. Another patient with persistent carcinoma *in situ* (CIS) received intravesical BCG treatment and remained disease-free after one year of follow-up. In 3 patients with persistent T1 disease, no further therapy other than TUR was applied due to advanced age, co-morbidity and non-compliance, and all died of progressive disease. Another patient with superficial Ta recurrence was lost to follow-up. Thus, overall progression occurred in 3 out of 5 patients who did not achieve a pCR after RCT and could not be salvaged by cystectomy. The 3 patients in whom re-staging TURB could not be performed were neither classified as responders nor as non-responders, however 2 of them remained free of disease at 31 and 35 months, and the other one developed a Ta tumor which was successfully managed with intravesical therapy, but died of another cause at 55 months.

Of the 55 CR patients, 8 (14.5%) showed progression, 7 (12.7%) experienced a superficial relapse and 40 (72.7%) have remained continously free of tumor. One patient developed distant metastasis without a bladder recurrence. At the last follow-up, 6 out of 8 patients with progression died of bladder cancer; in those patients, median time to progression was 34 (range; 9-121) months. None of the patients with superficial relapse had disease progression. The progression-free survival periods of pCR patients, as well as the related progression rates according to tumor characteristics, are shown in Table II. None of these factors were related to progression, and the progression-free survival of older patients was significantly lower than that of younger ones ($p=0.04$). Of those CR patients, 84.4% maintained their own bladders and 8 patients died of intercurrent diseases. The estimated five-year overall and disease-free survival rates were 76% and 93%, respectively.

Typical acute radiation-induced side-effects such as transient urocystitis and enteritis were easily managed by symptomatic treatment. There was no mortality due to systemic chemotherapy. During the course of follow-up, 4 patients suffered from reduced bladder capacity, and 2 patients underwent cystectomy due to a shrinking bladder. Radiotherapy- and chemotherapy-related side-effects are shown in Table III.

Discussion

The management of T1G3 bladder cancer is a challenge for the clinician. Current treatment options include early cystectomy or organ preservation by adjuvant intravesical therapy after TURB. The major goal of the treatment should be bladder preservation when possible, but not at the risk of death from metastatic TCC. Radiochemotherapy is a novel treatment strategy for T1G3 patients. According to the current literature, our RCT series represents the first and largest group of T1G3 patients with such a long-term follow-up. We demonstrate, in this series, that the RCT protocol can be safely performed for patients with T1G3 bladder cancer. Complete response was achieved in 90.2% of patients and superficial non-invasive relapses were successfully managed by local therapies. For initial non-responders and patients with invasive relapse, salvage cystectomy could still be performed. In the present series, 8 (12.5%) patients were salvaged by cystectomy. The irradiated preserved bladder functioned well, mild and transient side-effects of radiation were easily treated with local symptomatic therapies, and only 2 cystectomies (3%) were required due to a shrinking bladder.

Intravesical therapy after TUR has been reported to significantly reduce recurrences in high risk T1 cancers, however, it is not clear yet whether intravesical therapy, especially with BCG, has an effect on long-term progression (1). Although the results of a recent meta-analysis showed that the risk of progression to muscle-invasive disease is significantly reduced in papillary superficial TCC and CIS when BCG maintenance is used (14), it can not be concluded that intravesical BCG with

maintenance is the best treatment option for T1G3 tumors, as this meta-analysis included a very heterogeneous group of patients with only 7% of tumors with grade 3 differentiation. The optimal dose and scheme of maintenance therapy has not been determined yet, and additional toxicity is associated with additional therapy. In a previous series of BCG maintenance therapy, only 16% of 243 patients could complete all maintenance courses (15). Moreover, it remains to be proven whether adjuvant treatment with BCG results in a survival benefit, especially in the long run, for T1G3 patients. Although different selection criteria in most of the previous series make it difficult to interpret the results with regard to progression or disease-specific survival, the progression and survival figures in the present study are comparable to the results of other series using TUR plus intravesical BCG or primary cystectomy (Table IV) (2-8, 16-24). In the present series, the ultimate progression rate was restricted to 14% at five years, which compares favourably to most BCG studies.

Pathological assessment of the TUR specimen is an important task and considerable staging errors have been documented in recent series of T1G3 tumors. In a previous multicenter study, the pathological re-assessment of bladder biopsies diagnosed initially as stage T1G3 tumors resulted in a 50% change of diagnosis, including 10% of specimens that were re-classified as muscle-invasive disease (25). The rate of clinical understaging was as high as 40% in previous non-muscle invasive cystectomy series (5). Given the possibility that at the time of TURB the primary tumor may be clinically understaged and superficial cancer may have already invaded into the deep muscle wall, adding radiotherapy could exert certain advantages over intravesical instillation therapies, because deeper cell deposits can be more effectively treated by radiotherapy. In a recent prospective non-randomized study comparing the effectiveness of TUR plus intravesical therapy, TUR plus external radiotherapy and TUR alone, radiotherapy was found to be at least as effective as intravesical therapy (BCG or mitomycin-C) in T1G3 bladder cancer (26). In that study, 25% of patients treated with TUR plus intravesical therapy developed a recurrence with progression, whereas only 17% of the patients treated with TUR plus radiotherapy developed a recurrence with progression. Synergistic and sensitizing effects of concurrent chemotherapy may further exert local anti-tumoral efficacy as well aiding in eradicating occult systemic micrometastasis that is already present at the initiation of treatment. Approximately 5% of pT1 bladder tumors have regional nodal metastasis at presentation (27). Because eradication of lymph node metastasis is impossible with local intravesical therapies, concurrent RCT may be advantageous in these patients as well. As concurrent cisplatin-based chemotherapy has been shown to significantly increase local control and long-term survival in our series of patients treated for muscle-invasive diseases (9, 11), and also improved disease-specific survival in the present study, we recommend the use of concomitant RCT in T1G3 bladder cancer.

To date, there are no randomized studies investigating whether RCT is as effective as or even superior to current intravesical treatment options. Thus, without conducting a randomized trial, the answer to this question will remain unclear. It should be borne in mind that T1G3 bladder cancer patients are at life-long risk of disease recurrence or progression. As shown previously, the risk increases with increasing follow-up (24). Therefore, we believe that rigorous surveillance with long-term follow-up is mandatory for managing these cases.

Although our approach is complex and requires close cooperation between urologists and radiation oncologists, we have shown that high success rates are achieved with such an approach. Thus, radiochemotherapy after TURB is a safe and curative treatment option for patients with T1G3 TCC of the bladder in the hands of dedicated multimodality teams. Therefore, it is reasonable to justify radiochemotherapy combined with TURB in the first-line treatment of T1G3 tumors.

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Received August 2, 2004
Accepted February 4, 2005