

Radiotherapy is an Effective Treatment for High-Risk T1-Bladder Cancer

Claus Rödel¹, Jürgen Dunst², Gerhard G. Grabenbauer¹, Reinhard Kühn³, Thomas Papadopoulos⁴, Karl Michael Schrott³, Rolf Sauer¹

Purpose: Current treatment options for high-risk superficial T1-bladder cancer (Grade 3, associated Tis, multifocality, tumor diameter > 5 cm or multiple recurrences) include early cystectomy or the goal of organ preservation by adjuvant intravesical therapy after transurethral resection (TURB). We have evaluated the efficacy of adjuvant radiotherapy or radiochemotherapy on local control, bladder preservation, recurrence rate and long-term survival after TURB of high-risk T1-bladder cancer.

Patients and Methods: From May 1982 to May 1999, a total of 74 patients with T1-bladder cancer were treated by either radiotherapy (n = 17) or concomitant radiochemotherapy (n = 57) after TURB. Radiotherapy was initiated 4 to 8 weeks after TURB; a median dose of 54 (range: 45 to 60) Gy was applied to the bladder with daily fractions of 1.8 to 2.0 Gy. Since 1985 chemotherapy has been given in the 1st and 5th week of radiotherapy and consisted of cisplatin (25 mg/m²/d) in 33 patients, carboplatin (65 mg/m²/d) was administered in 14 patients with decreased creatine clearance (< 50 ml/min). Since 1993 a combination of cisplatin (20 mg/m²/d) and 5-fluorouracil (600 mg/m²/d) was applied to 10 patients. Salvage cystectomy was recommended for patients with refractory disease or invasive recurrences. At the time of analysis, the median follow-up for surviving patients was 57 (range: 3 to 174) months.

Results: After radiotherapy/radiochemotherapy, a complete remission at restaging TURB was achieved in 62 patients (83.7%), 35 of whom (47% with regard to the total cohort of the 74 treated patients) have been continuously free of tumor, 11 patients (18%) experienced a superficial relapse and 16 patients (26%) showed tumor progression after initial complete response. Overall-survival was 72% at 5 years and 50% at 10 years with 77% of the surviving patients maintaining their own bladder at 5 years. Negative prognostic factors for cancer-specific survival were non-complete (R1/2) initial TURB (p = 0.12) and recurrent disease (p = 0.07); combined radiochemotherapy was more effective than radiotherapy alone (p = 0.1).

Conclusion: Adjuvant radiotherapy/radiochemotherapy offers an additional option in high-risk superficial bladder cancer with a high chance of cure and bladder preservation. The ultimate value of radiotherapy in comparison with other treatment options should be determined in randomized trials.

Key Words: High-risk T1-bladder cancer · Radiotherapy · Bladder preservation

Strahlenther Onkol 2001;177:82–8
DOI 10.1007/s00066-001-0810-x

Radiotherapie als effektive Behandlung bei T1-Blasenkarzinomen mit hohem Rezidivrisiko

Hintergrund: Die gegenwärtigen Behandlungsoptionen beim oberflächlichen T1-Blasenkarzinom mit hohem Rezidivrisiko (G3, assoziiertes Tis, Multifokalität, Größe > 5 cm, multiple Rezidive) umfassen die sofortige Zystektomie oder die transurethrale Resektion (TURB) mit adjuvanter intravesikaler Therapie zum Zweck des Organerhalts. Wir haben die Wirksamkeit einer adjuvanten Radio- oder Radiochemotherapie bezüglich lokaler Kontrolle, Blasenenerhalt, Rezidivrate und Langzeitüberleben bei T1-Blasenkarzinom mit hohem Risikoprofil untersucht.

Patienten und Methoden: Von Mai 1982 bis Mai 1999 wurden 74 Patienten mit Hochrisiko-T1-Blasenkarzinom nach TURB bestrahlt (n = 17) oder radiochemotherapiert (n = 57). Die Radiotherapie begann vier bis acht Wochen nach TURB; im Median wurden 54 Gy (Spanne: 45 bis 60 Gy) mit einer Einzeldosis von 1,8 bis 2,0 Gy auf die Blase verabreicht. Seit 1985 erfolgte eine simultane Chemotherapie in der ersten und fünften Radiotherapiewoche mit Cisplatin (25 mg/m²/Tag) bei 33 Patienten, 14 Patienten mit reduzierter Kreatininclearance (< 50 ml/min) erhielten Carboplatin (65 mg/m²/Tag). Seit 1993 wurde eine Kombination von Cisplatin (20 mg/m²/Tag) und 5-Fluorouracil (600 mg/m²/Tag) bei 10 Patienten eingesetzt. Die Salvage-Zystektomie wurde für Patienten mit refraktärem Karzinom oder invasivem Rezidiv empfohlen. Zum Auswertzeitpunkt war die mediane Nachbeobachtungszeit für die überlebenden Patienten 57 Monate (Spanne: drei bis 174 Monate).

¹ Department of Radiation Oncology, University of Erlangen, Germany,

² Department of Radiation Oncology, University of Halle, Germany,

³ Department of Urology and

⁴ Institute of Pathology, University of Erlangen, Germany.

Submitted: July 17, 2000; accepted: November 10, 2000.

Ergebnisse: Eine komplette Remission bei der Restaging-TURB nach Radiotherapie/Radiochemotherapie wurde bei 62 Patienten (83,7%) erreicht, von denen 35 (47% bezogen auf die Gesamtzahl der 74 behandelten Patienten) im weiteren Verlauf tumorfrei blieben; elf Patienten (18%) erlitten ein oberflächliches Rezidiv, 16 Patienten (26%) zeigten eine Tumorprogression nach initialer kompletter Remission. Das Gesamtüberleben nach fünf Jahren betrug 72%, nach zehn Jahren 50%; 77% der nach fünf Jahren überlebenden Patienten konnten ihre Blase erhalten. Prognostisch ungünstige Faktoren bezüglich des krankheitsspezifischen Überlebens waren eine nicht radikale (R1/2) initiale TURB ($p = 0,12$) und eine Behandlung nach multiplen Rezidiven ($p = 0,07$). Die kombinierte Radiochemotherapie war effektiver als die alleinige Bestrahlung ($p = 0,1$).

Schlussfolgerung: Die adjuvante Radiotherapie/Radiochemotherapie ist eine alternative Behandlungsoption bei oberflächlichen Hochrisikoblaskarzinomen mit hoher Heilungsrate und Blasenerhalt. Der Stellenwert der Radiotherapie im Vergleich zu anderen Behandlungsmethoden sollte in randomisierten Studien überprüft werden.

Schlüsselwörter: Hochrisiko-T1-Blaskarzinom · Radiotherapie · Blasenerhalt

Introduction

Superficial bladder cancer carries a relatively favorable prognosis in most cases. Non-invasive papillary tumors (Ta) and superficially infiltrating cancers with high or moderate differentiation (T1 G1–2) can often be managed successfully by transurethral resection. Patients in whom superficial tumors are less differentiated (G3), large, multiple, or associated with carcinoma in situ (Tis) are at greater risk of recurrent disease and tumor progression. The treatment recommendations for these high-risk superficial tumors differ widely. Some authors go on to favor radical cystectomy [1, 9, 25], whereas most of the recent series propose an organ-preserving approach, including TUR with fulguration followed by intravesical BCG or intravesical chemotherapy with thiotepa, mitomycin or doxorubicin [10, 11, 15, 17].

Intravesical therapy after transurethral resection has been reported to significantly reduce recurrences in these high-risk superficial cancers, however, it also became evident that it mainly reduces favorable recurrences while it had only a limited effect on progression of disease [17]. Moreover, it remains unclear whether adjuvant treatment with BCG results in a survival benefit especially in the long run. The American Urological Association has recently published treatment recommendations for superficial bladder cancer on the basis of a metaanalysis of studies with intravesical therapy. According to this analysis, all types of drugs may reduce the rate of recurrences and intravesical therapy is therefore recommended for T1 and high-risk Ta tumors after transurethral removal of the tumor. However, the recommendations include the remark that there is no effect of intravesical therapy on long-term progression [24].

Urothelial cancers are sensitive to radiation. The doses necessary to control microscopic disease lie in the range of 45 to 50 Gy. These doses are far below the tolerance dose of the bladder (about 60 Gy for whole bladder irradiation) and can therefore be administered to a large volume with minimal risk of severe side effects. It has been the ongoing policy at the University of Erlangen to use radiotherapy with or without concurrent chemotherapy with platin derivatives for invasive bladder cancer in a prospective protocol since 1982 [2, 3, 7, 20,

22]. Herein, we report on our results in 74 patients with high-risk T1-bladder cancer treated by a combined modality program including TURB and adjuvant radiotherapy/radiochemotherapy with emphasis on local control, bladder-preservation and long-term survival.

Patients Characteristic and Treatment Protocol

Between May 1982 and May 1999, a total of 74 patients suffering from primary or recurrent high-risk T1-bladder cancer were treated with either radiotherapy or concomitant radiochemotherapy after initial transurethral resection (TURB). Risk factors for T1 cancer were defined as tumor Grade 3, associated Tis, multifocality, a tumor diameter > 5 cm or multiple recurrences. No patient had evidence of pelvic lymph node metastases on pretreatment computed tomography or ultrasound and all patients were free of distant metastases at the time of onset of radiotherapy/radiochemotherapy. Multiple TURBs prior to radiotherapy/radiochemotherapy or poor general condition with contraindications for radical cystectomy were not exclusion criteria. Patients' and tumor characteristics are shown in Table 1.

Treatment was commenced by TURB aimed at maximal, if feasible complete resection of the tumor mass. Residual tumor was assessed histologically by biopsies from all resection margins: R0 indicated microscopically complete TURB, R1 microscopic tumor residual, R2 macroscopic tumor residual. T category and grade were assessed according to the TNM classification of 1992 (UICC). Radiotherapy 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 54 (range 45 to 60) Gy was applied to the bladder, the pelvis was irradiated with a median dose of 45 (range 36 to 50.4) Gy. Eighteen patients additionally received a median dose of 45 (range 36 to 45) Gy to the paraaortic lymph nodes. Seventeen patients were treated by radiotherapy alone. As of October 1985, chemotherapy has been given simultaneously with radiotherapy. Chemotherapy was applied in the 1st and 5th week of radiotherapy and consisted of cisplatin (25 mg/m²/d)

Table 1. Patients' and tumor characteristics in 74 patients with high-risk T1-bladder cancer.

Tabelle 1. Patienten- und Tumorcharakteristik bei 74 Patienten mit Hochrisiko-T1-Blasenkarzinom.

Median age (range) (years)	64 (31-83)
Sex (male/female)	65/9
Primary tumor	49
Recurrent tumor	25
Grading	
G2	31
G3	43
Associated Tis	
Yes	26
No	48
Multifocal tumor	
Yes	39
No	35
Lymph-vessel involvement	
Yes	15
No	59
R status after TURB	
R0	33
R1	28
R2	13

in 33 patients, carboplatin (65 mg/m²/d) was administered in 14 patients with decreased creatine clearance (< 50 ml/min) or congestive heart disease. Since 1993 a combination of cisplatin (20 mg/m²/d) and 5-fluorouracil (600 mg/m²/d) was applied to 10 patients.

Six to 8 weeks after completion of radiotherapy/radiochemotherapy, the response quality was evaluated by deep TURB of the former tumor bed. In case of histologically proven complete response, patients were followed at 3-month intervals, including cystoscopy and biopsies of all suspected

areas. In cases of persistent or recurrent invasive tumor, salvage cystectomy was recommended.

All patients were followed up until May 1999. At the time of analysis, the median follow-up for all surviving patients was 57 months (range, 3 to 174). Thirty-one patients have been followed up 5 years and more. Survival rates were calculated according to the Kaplan-Meier method, differences were tested for statistical significance by the log rank test.

Results

Initial Response

Initial TURB provided a complete resection (R0) in 44.6% (33 of 74 patients). After radiotherapy/radiochemotherapy, a complete remission (CR) at restaging TURB was achieved in 62 patients (83.7%, Figure 1). Following R1 and R2 resection CR was 89.3% (25 of 28 patients) and 46.2% (6 of 13 patients), respectively. In 2 of the 33 patients with R0 resection at initial TURB a Ta tumor was found at restaging TURB. With radiotherapy alone CR was 80%, with radiochemotherapy 84% (n. s.). Three patients had persistent superficial Ta tumor at restaging TURB, 4 patients Tis and 5 patients persistent T1 tumor. Immediate salvage cystectomy was successfully performed in 3 of 5 patients with persistent T1 tumor, all of them remained free of tumor until the last follow-up 2.7 and 8 years post cystectomy. In 2 patients with persistent T1 cancer no further therapy was applied due to advanced age and comorbidity, 1 patient died without tumor progression 1 year after treatment and the other one died of distant metastases 30 months after radiotherapy. In patients with persistent superficial Tis tumor, salvage cystectomy was performed in 1 patient (being alive without evidence of disease since 35 months), instillation therapy in 2 (1 developed distant disease, the other a superficial relapse), and no further therapy in 1 patient who is alive with no evidence of disease 6 years post treatment. In 1 of 3 patients with persistent Ta disease the tumor ultimately progressed. Thus, overall progression rate for patients who did

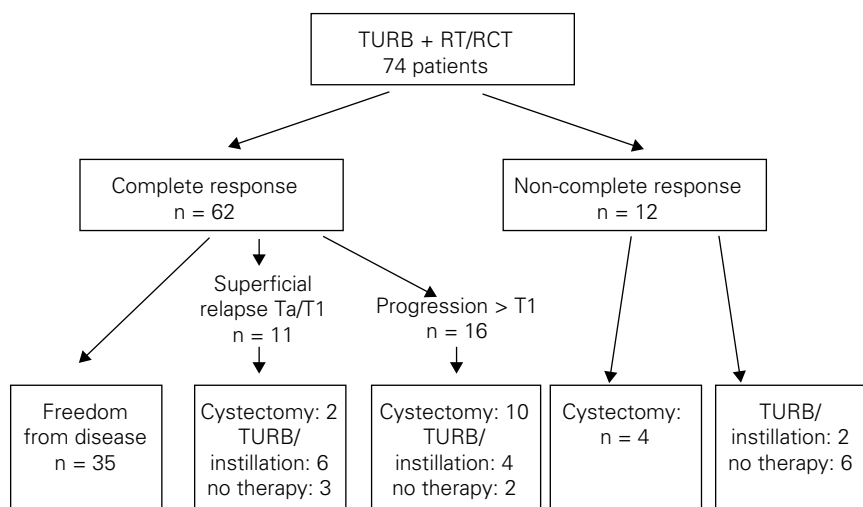


Figure 1. Local control, superficial relapse and progression in 74 patients treated with TURB and radiotherapy/radiochemotherapy.

Abbildung 1. Lokale Kontrolle, oberflächliche Rezidive und Tumorprogression bei 74 Patienten, die nach TURB eine Radiotherapie/Radiochemotherapie erhielten.

not achieve a complete response (n = 12) after radiotherapy/radiochemotherapy and could not be salvaged by prompt cystectomy (n = 4) was 50% (4 of 8 patients), indicating the dismal prognosis of non-responding, thus biologically unfavorable tumors.

Local Control, Superficial and Invasive Recurrences

Among 62 patients who had no evidence of disease at restaging TURB, 35 patients (56%) have been continuously free of tumor: 20 of 33 patients (60.6%) with initial R0 resection, 14 of 28 patients (50%) with initial R1 and 2 of 13 patients (15.4%) with initial R2 resection. In the radiotherapy alone and radiochemotherapy group 5 of 17 patients (29.4%) and 30 of 57 patients (52.6%), respectively, remained free of tumor. Eleven patients (18%) experienced a superficial relapse ($\leq T1$) and 16 patients (26.%) showed tumor progression (T1 or distant metastases, see Figure 1). In 12 of these 27 patients with recurrent disease, salvage cystectomy could be performed, 10 patients with advanced age were managed conservatively with TUR and/or mitomycin instillation and in 5 patients no further therapy was applied. At the last follow-up in may 1999, 8 of 12 patients who underwent salvage cystectomy had no evidence of disease, after conservative treatment 5 of 10 patients ultimately progressed. Thus, for the total number of patients (n = 74), 35 patients (47.3%) were cured by TURB and radiothera-

py/radiochemotherapy, 12 patients (16.2%) were successfully salvaged by cystectomy, 9 patients (12.2%) with persistent or recurrent disease that was managed conservatively, were free of tumor at the last follow-up, and 18 patients (24.3%) ultimately progressed.

Survival and Bladder Preservation

Overall survival and cause-specific survival for all patients were 72% and 82% at 5 years and 50% and 66% at 10 years, respectively. Of all surviving patients, 77% and 67% maintained their own and well-functioning bladder at 5 and 10 years, respectively (Figure 2). Cause-specific survival after 5 and 10 years was 61% and 49% for radiotherapy and 89% and 72% for radiochemotherapy (p = 0.1; Figure 3). Patients with recurrent tumors had a worse prognosis than patients treated for primary T1 tumors (p = 0.07, Figure 4). Completeness of TUR prior to radiotherapy/radiochemotherapy was also an important, albeit not statistically significant (p = 0.12) prognostic factor (Figure 5). None of the other risk factors (grading, associated TIS, multifocality and lymph-vessel involvement) influenced cause-specific survival.

Acute and Late Toxicity

Typical acute radiation-induced side effects, such as transient urocystitis and enteritis, were easily managed by symptomatic

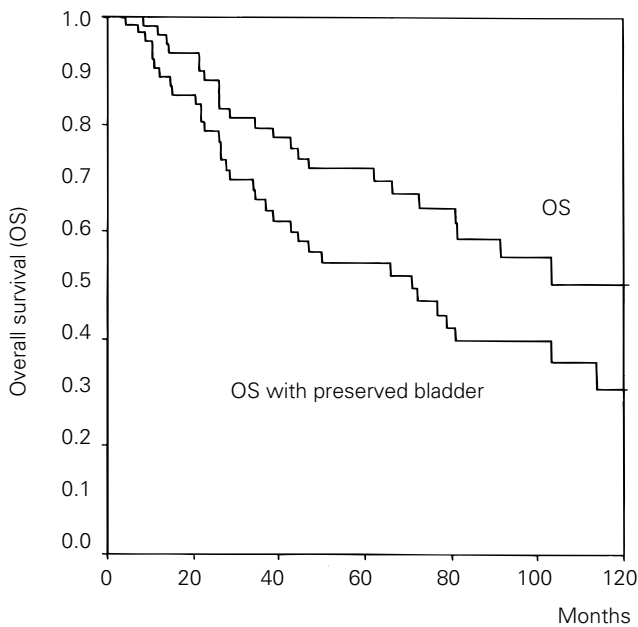


Figure 2. Overall survival and overall survival with preserved bladder. In the lower plot, salvage cystectomy was taken as an additional event.

Abbildung 2. Gesamtüberleben und Gesamtüberleben mit Blasenerhalt. In der unteren Kurve wurde die Salvage-Zystektomie als zusätzliches Ereignis gewertet.

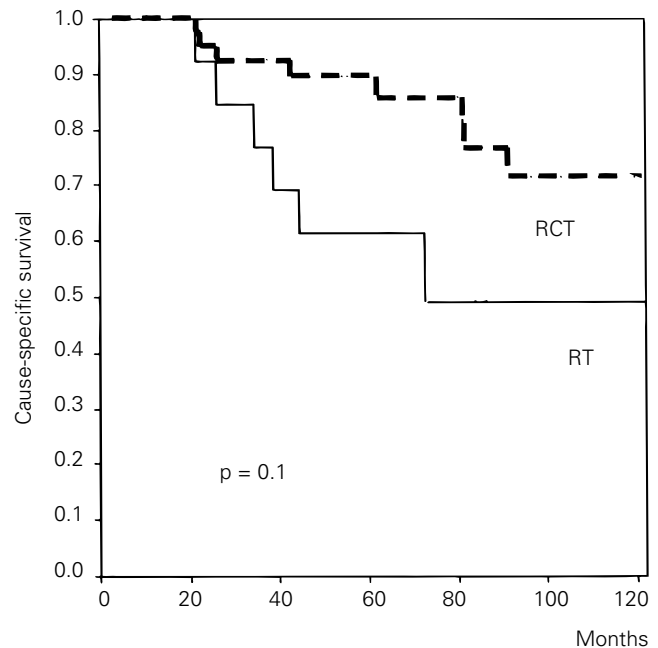


Figure 3. Cause-specific survival according to treatment: RT = radiotherapy (n = 17 patients), RCT = concurrent radiochemotherapy (n = 57 patients).

Abbildung 3. Krankheitsspezifisches Überleben nach Therapiemodalität: RT = Radiotherapie (n = 17 Patienten), RCT = kombinierte Radiochemotherapie (n = 57 Patienten).

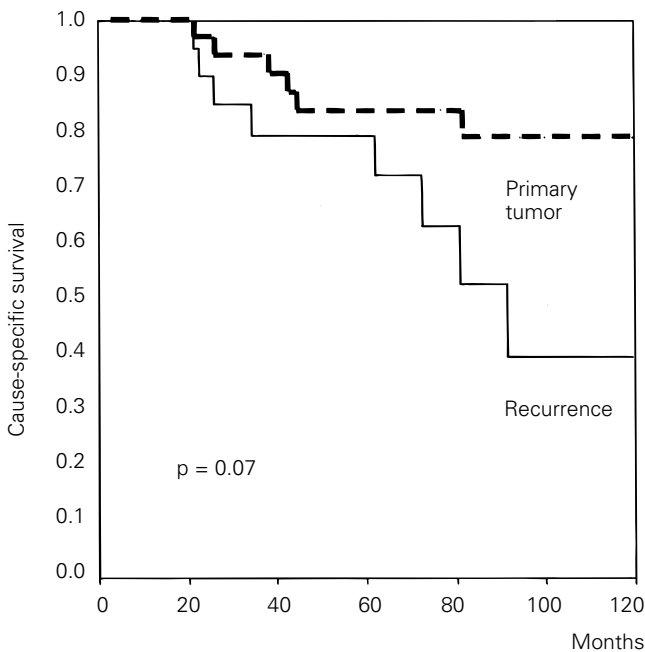


Figure 4. Cause-specific survival for patients treated for primary (n = 49 patients) or recurrent disease (n = 25 patients).

Abbildung 4. Krankheitsspezifisches Überleben für Patienten mit Primär- (n = 49 Patienten) oder Rezidivtumoren (n = 25 Patienten).

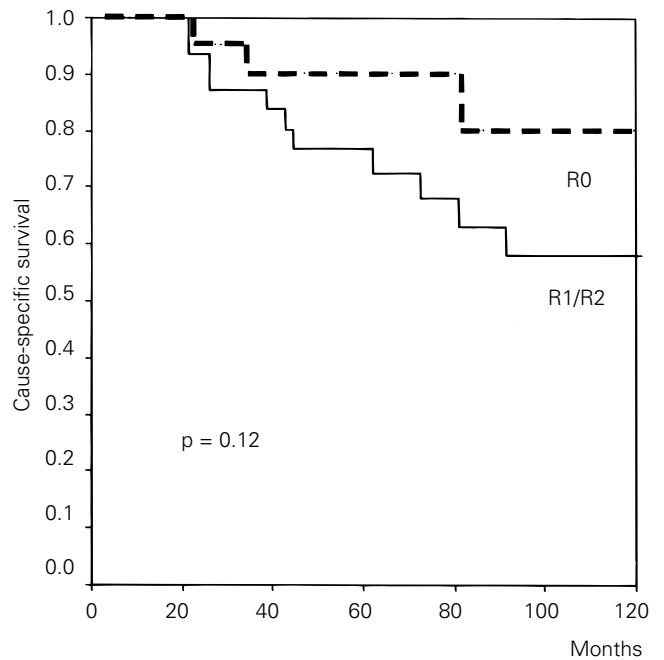


Figure 5. Cause-specific survival according to resection status at TURB: R0 = no residual disease (n = 33 patients), R1/R2 = microscopic/macroscopic residual disease (41 patients).

Abbildung 5. Krankheitsspezifisches Überleben nach Resektionsstatus der TURB: R0 = kein verbliebener Resttumor (n = 33 Patienten), R1/R2 = mikroskopischer/makroskopischer Resttumor (n = 41 Patienten).

treatment. Twenty-nine percent of the patients receiving CT experienced WHO Grade 3 and 1% Grade 4 hematological toxicity. In 1 patient late gastrointestinal toxicity WHO Grade 4 occurred. This patient suffered from necrotizing enteritis, underwent resection and is free of complications at the last follow-up. One patient underwent cystectomy due to shrinking bladder following multiple (n = 12) TURBs before radiotherapy.

Discussion

The theoretical background for the use of radiotherapy as a treatment component in high-risk superficial bladder cancer arises from the proven efficacy of radiotherapy against urothelial cancer. In more advanced muscle-invasive disease, several groups have reported the value of combined modality treatment, including TURB, radiation therapy and concurrent chemotherapy with survival figures comparable to cystectomy-based series and bladder preservation in 80% of the long-term survivors [4, 5, 14, 16, 20, 23]. Given the possibility that, at the time of TURB, the primary tumor may be clinically understaged in superficial cancer and may have already invaded into the deep muscle wall, radiotherapy should exert certain advantages over intravesical instillation therapy. This understaging error lies probably in the range of 20 to 30%. Cell deposits in the muscle wall are surely not adequately

treated by intravesical instillation therapy, which may also explain the phenomenon that intravesical chemo- or immunotherapy mainly reduces the risk of superficial but not of deep muscle-invasive recurrences. With external beam radiotherapy, conversely, deeper cell deposits can be adequately treated.

Most of the radiotherapy series in the literature contain patients with muscle-invading cancers and only few superficial tumors. The referral of a patient with superficial cancer to radiotherapy probably reflects some kind of negative selection with regard to prognostic factors such as age, general condition, resectability or recurrence. Nevertheless, the survival figures in our series with death rates from bladder cancer at 5 and 10 years from 18% and 34%, respectively, and a progression rate of 26% for those patients who achieved a complete response after radiotherapy/radiochemotherapy are comparable to the results of other large series using TUR + intravesical therapy (Table 2). Moreover, 77% of the 5-year survivors and 67% of the 10-year survivors maintained their own and well-functioning bladder. To our knowledge, there is no other series with a comparable high rate of organ preservation in long-term survivors beyond 5 years.

Interestingly, in our study, tumor differentiation (G2/G3) and the presence of associated Tis did not show any impact on treatment outcome. The results of the 43 patients with T1G3

Table 2. Treatment outcome after conservative treatment of T1G3-bladder cancers with TUR + BCG (n = number of patients; n.d. = not determined).

Author	n	Treatment	Follow-up (years)	Progression rate	Deaths from bladder cancer
Eure et al. 1992 [8]	30	TUR + BCG	< 5	17%	n.d.
Cookson et al. 1992 [6]	16	TUR + BCG	< 5	19%	n.d.
Pansadoro et al. 1995 [19]	50	TUR + BCG	< 5	12%	n.d.
Zhang et al. 1996 [26]	23	TUR + BCG	< 5	35%	22%
Hurle et al. 1996 [13]	51	TUR + BCG	< 5	14%	12%
Sarkis et al. 1993 [21]	43	TUR	10	51%	30%
Holmang et al. 1995 [12]	58	TUR	20	45%	36%
Herr 1997 [10]	48	TUR + BCG	15	52%	31%

Tabelle 2. Behandlungsergebnisse nach konservativer Therapie des T1G3-Blasenkarzinoms mit TUR + BCG (n = Anzahl der Patienten; n.d. = nicht bestimmt).

cancers were not different from those of T1G2 cancers treated for other risk factors, such as multifocality, refractory disease or lymph-vessel involvement. This finding is important with regard to the question how to define a high-risk subgroup within the population of patients with superficial cancers. Evidently, T1G3 is not the only risk group. We found that important prognostic factors regarding long-term survival were a) whether patients were treated for primary or recurrent T1 cancer (p = 0.07) and b) the completeness of primary TURB (R0 vs R1/2, p = 0.12). Thus, it is to be expected that survival figures of patients with high-risk T1-bladder cancer would further increase, if patients would receive definitive radiotherapy/radiochemotherapy as early as possible rather than in refractory or recurrent disease. Moreover, a resection of the tumor as thorough as safely possible, if necessary by multiple re-TURBs, should be performed prior to radiotherapy/radiochemotherapy to achieve an R0 status. The significant number of patients with residual tumor in our series might be explained by the high percentage of multifocal tumor (53%) and by the fact that, in the beginning of our trial in the early 80s, re-TURBs were not consequently performed. 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 disease [20, 22], and also improved cancer-specific survival in this present study, we recommend to apply concomitant radiochemotherapy in high-risk T1 cancer whenever feasible, particularly in poor prognostic subgroups such as patients, in which a complete resection of the tumor by initial TURB cannot be accomplished, and in patients with recurrent or refractory disease.

Up to now, there are no randomized trials addressing the question whether radiotherapy is as effective or superior to current intravesical treatment options. However, the Dutch South Eastern Bladder Cancer Group has recently presented data in 121 patients with T1G3 cancers [18]. This series is the largest group of T1G3 cancers that has ever been published in a single series. External radiotherapy with 50 Gy was one treatment option and 17 patients received radiotherapy. Radiotherapy was as effective as intravesical BCG or mitomycin C and yielded (in absolute figures) the best results (Table 3).

Table 3. Impact of adjuvant intravesical therapy or radiotherapy after TUR on patterns of recurrence and time to progression in T1G3-bladder cancer. Prospective, non-randomized data from the Dutch South Eastern Bladder Cancer Study [18].

Tabelle 3. Einfluss einer adjuvanten intravesikalen Therapie oder Radiotherapie nach TUR auf das Rezidivmuster und die Zeit bis zur Progression bei T1G3-Blasenkarzinom. Prospektive, nicht randomisierte Daten der Dutch South Eastern Bladder Cancer Study [18].

Treatment	n	Time to recurrence (months)	Recurrences without progression	Recurrences with progression
TUR only	48	11	48%	27%
TUR + BCG or TUR + MMC	51	19	30%	25%
TUR + XRT	17	25	18%	17%

Conclusion

A relevant subset of patients with superficial bladder cancer are at very high risk for recurrent and progressive cancers over a long period. Current treatment options include early cystectomy or the goal of organ preservation by adjuvant intravesical therapy after TUR. Adjuvant radio(chemo-)therapy offers an additional option with a high chance of cure and bladder preservation. Currently, radiotherapy is indicated in patients with superficial cancers with a high risk for recurrence and progression, especially in patients with multiple risk factors who are unfit for cystectomy or seek bladder preservation. The ultimate value of radiotherapy in comparison with other treatment options should be determined in randomized trials. As the incidence of this subset of bladder cancer is limited, however, a multicenter study would certainly be necessary to recruit enough patients.

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Address for Correspondence

Dr. Claus Rödel
 Department of Radiotherapy, University
 Universitätsstraße 27
 D-91054 Erlangen
 Germany
 Phone (+49/9131) 853-4090, Fax -9335
 e-mail: claus.roedel@strahlen.med.uni-erlangen.de