

# Organ-Sparing Treatment in Muscle-Invasive Bladder Cancer

Jürgen Dunst<sup>1</sup>, Andrea Diestelhorst<sup>1</sup>, Reinhard Kühn<sup>2</sup>, Arndt-Christian Müller<sup>1</sup>, Hans-Jörg Scholz<sup>3</sup>, Paolo Fornara<sup>4</sup>

**Background and Purpose:** Organ-sparing treatment of bladder cancer by a trimodality approach is feasible and effective. In this study, the results of a series of patients are reported, who were, in the majority, not suitable for major surgery.

**Patients and Methods:** In the period from June 1995 through December 2003, 68 patients (64 males, four females) with urothelial bladder cancer were treated with curative intent. The median age was 68 years (range 42–82 years). Clinical T-category was 32× T2, 20× T3, and 16× T4. Transurethral resection was performed in all cases, and a complete TUR-BT (transurethral resection of bladder tumor) was attempted, if possible. Radiotherapy was administered in conventional fractionation (five fractions of 1.8 Gy per week) up to 50.4 Gy to bladder, and regional nodes and the whole bladder received a boost up to 54–59.4 Gy. 34 patients received concurrent cisplatin-based chemotherapy (25 mg/m<sup>2</sup> on days 1–5 and 29–33), and patients with impaired renal function were either treated with irradiation alone (n = 7) or received paclitaxel as alternative to cisplatin in a phase II protocol or on an individual decision (n = 27). The median follow-up was 34 months (range 2–104 months).

**Results:** A histologically confirmed complete remission (CR) on restaging cystoscopy was observed in 40/46 patients (87%) who underwent restaging cystoscopy. CR rates were not significantly correlated to T-category (CR: 24/32 T2, 9/19 T3, and 9/16 T4 tumors) or clinical nodal status. Patients with non-radical resection and macroscopic residual tumor (R2 resection) achieved a CR in only 39% (12/31); this figure was significantly lower as compared to patients with radical R0 TUR-BT (CR: 15/16, 94%, p = 0.013). Furthermore, age and preexisting anemia had no impact on response. The overall survival of the whole group was 45% after 5 years, and survival according to clinical T-category was 62% for T2, 43% for T3, and 19% for T4 (p = 0.015). In eleven patients, local disease progression or relapse was observed. So far, only one salvage cystectomy has been performed, due to contraindications to surgery in the majority of patients.

**Conclusion:** The data obtained in this study confirm the high efficacy of TUR and radiochemotherapy for locally advanced bladder cancer.

**Key Words:** Bladder cancer · Radiotherapy · Chemotherapy

Strahlenther Onkol 2005;181:632–7  
DOI 10.1007/s00066-005-1416-5

## Organerhaltende Behandlung des muskelinvasiven Harnblasenkarzinoms

**Hintergrund und Ziel:** Die organerhaltende Behandlung des lokal fortgeschrittenen Harnblasenkarzinoms hat sich in prospektiven Studien als effektive Maßnahme erwiesen. In dieser Studie werden retrospektive Daten der eigenen Klinik an einem ungünstig selektionierten Kollektiv primär nicht zystektomiefähiger Patienten vorgestellt.

**Patienten und Methodik:** Von Juni 1995 bis Dezember 2003 wurden an der eigenen Klinik 68 Patienten (64 Männer, vier Frauen) mit Urothelkarzinomen der Harnblase in kurativer Intention mit einer Radiotherapie oder Radiochemotherapie behandelt. Der weit überwiegende Teil der Patienten wurde bei lokaler oder funktioneller Inoperabilität zur Strahlentherapie überwiesen. Das mittlere Alter betrug 68 Jahre (Spanne 42–82 Jahre). Die klinische T-Kategorie war 32× T2, 20× T3 und 16× T4. Alle Patienten hatten eine möglichst komplette transurethrale Resektion (TUR). Die Radiotherapie erfolgte in konventioneller Fraktionierung (fünfmal wöchentlich 1,8 Gy) bis zu einer Gesamtdosis von 50,4 Gy an Blase und Lymphknoten; die ganze Blase wurde bis 54 Gy (R0-TUR) bzw. 59,4 Gy (R1–2-TUR) aufgesättigt. 34 Patienten erhielten eine simultane Chemotherapie mit Cisplatin (25 mg/m<sup>2</sup> an den Tagen 1–5 und 29–33), und Patienten mit eingeschränkter Nierenfunktion erhielten entweder eine alleinige Strahlentherapie (n = 7) oder wurden im Rahmen eines Phase-II-Protokolls mit Paclitaxel als Ersatz für Cisplatin behandelt (n = 27). Die mediane Nachbeobachtungszeit betrug 34 Monate (Spanne 2–104 Monate).

<sup>1</sup> Department of Radiotherapy, Martin Luther University Halle-Wittenberg, Germany,

<sup>2</sup> Department of Urology, Martha Maria Hospital Halle, Germany,

<sup>3</sup> Department of Urology, Asklepios Hospital Weißenfels, Germany,

<sup>4</sup> Department of Urology, Martin Luther University Halle-Wittenberg, Germany.

Received: January 18, 2005; accepted: July 13, 2005

**Ergebnisse:** Von den 46 zystoskopisch und biotisch nachkontrollierten Patienten erreichten 40 (87%) eine komplette Remission (CR). Die klinischen CR-Raten waren unabhängig von der initialen T-Kategorie (CR: 24/32 T2-, 9/19 T3- und 9/16 T4-Tumoren) und dem klinischen Nodalstatus. Patienten mit nicht-radikaler TUR und makroskopischem Resttumor (R2-TUR) erreichten in 39% eine CR (signifikant verschieden von Patienten mit R0-TUR). Alter und prätherapeutische Anämie hatten keine Einfluss auf Remissionsrate und Überleben. Die Überlebensrate aller Patienten lag bei 45% nach 5 Jahren, und die Überlebensraten in Abhängigkeit von der T-Kategorie betragen 62% für T2, 43% für T3 und 19% für T4 ( $p = 0,015$ ). Bei elf Patienten trat eine lokale Tumorprogression oder ein Rezidiv auf. Bedingt durch die negative Selektion mit primär überwiegend inoperablen Patienten wurde bis jetzt nur bei einem Patienten eine Salvage-Zystektomie durchgeführt.

**Schlussfolgerung:** Die Daten dieser Studie bestätigen die Effektivität der Radiochemotherapie für fortgeschrittene Harnblasenkarzinome selbst bei eher ungünstiger Patientenselektion.

**Schlüsselwörter:** Blasenkarzinom · Radiotherapie · Chemotherapie

## Introduction

Organ preservation is feasible and effective in patients with muscle-invasive bladder cancer and offers an attractive alternative to radical cystectomy which has been considered the standard of care for this disease. Optimal results in terms of organ preservation are achieved, if radiotherapy is embedded in a multimodal approach including transurethral resection (TUR), irradiation plus concurrent cisplatin chemotherapy and salvage cystectomy for nonresponding or recurrent tumors [4, 8, 9, 16–18, 21, 22, 24]. There are no randomized studies directly comparing radical cystectomy and such multimodal organ-preserving protocols. However, numerous prospective studies using a bladder-preserving approach have reported survival figures comparable to cystectomy series [3].

A subset of patients with advanced bladder cancer is not suitable for radical cystectomy due to patient- (age, comorbidity) or tumor-related factors (local non-resectability). These patients, however, often tolerate a curative irradiation or radiochemotherapy regimen. On the other hand, the prognosis of locally advanced bladder cancer not only depends on tumor-related parameters, but also on patient-related factors such as performance status, age, and pretreatment hemoglobin level or sedimentation reaction (BSR) [4]. Therefore, patients unsuitable for major surgery represent per se a poorly selected high-risk population. It is likely that the prognosis of these patients is inferior to better selected groups. However, this subgroup of patients, according to data in the literature, can be cured by radiotherapy or radiochemotherapy with acceptable long-term survival figures [18, 19].

The objective of this article is to investigate the outcome of patients with muscle-invasive bladder cancer treated at a single institution.

## Patients and Methods

### Patient Population

In the period from June 1995 through December 2003, 68 patients (64 males, four females) with muscle-invasive urothelial bladder cancer were treated in our department with curative intent. 24 patients treated in the same period who had

non-urothelial histology ( $n = 4$ ), metastatic disease ( $n = 8$ ) or received low-dose palliative irradiation for symptoms ( $n = 12$ ) were excluded. The median age was 68 years (range 42–82 years). Furthermore, 14 patients were treated for recurrent superficial tumors in the same period, and treatment was administered as an alternative to radical cystectomy in these patients. This subgroup will also not be analyzed in this investigation.

All patients were referred from three urologic departments of which two used radical cystectomy as standard treatment for muscle-invasive bladder cancer. Thus, the majority of patients in this analysis are patients with either contraindications to major surgery (due to advanced age or comorbidity) or locally advanced tumors which were considered non radically resectable.

The distribution of major prognostic factors is listed in Table 1.

### Staging

The initial staging consisted of a transurethral resection of bladder tumor (TUR-BT, see below). After establishing the histological diagnosis of invasive or recurrent urothelial cancer, further staging procedures included a computed tomography (CT) or magnetic resonance imaging (MRI) of the pelvis and abdomen to detect extravesical spread and/or enlarged regional or paraaortic lymph nodes, CT or ultrasound examination of the liver to exclude liver metastases, a chest X-ray or thoracic CT to exclude lung metastases, and laboratory work-up.

### Treatment

#### Transurethral Surgery

TUR was performed in all cases, and a complete TUR-BT was attempted, if possible. In case of superficial or T2 tumors, a second TUR-BT was routinely performed to achieve a complete resection, if the first TUR-BT was non-radical.

29 patients (43%) had one, 21 (31%) two, and the remaining 18 patients (26%) three or more TUR-BTs prior to radiotherapy.

### Radiotherapy

All patients underwent CT-based treatment planning (mainly three-dimensional planning) plus treatment simulation at a simulator with instillation of contrast medium in bladder and rectum. Radiotherapy was administered with 10- to 15-MV photons via four individually shaped fields in conventional fractionation (five fractions of 1.8 Gy per week, doses refer to the ICRU reference point). The regional lymphatics were included up to 50.4 Gy in the majority of patients up to the aortic bifurcation; however, the upper field border was chosen lower in patients with advanced age in case of clinically uninvolved nodes (cN0) on an individual decision to improve treatment

**Table 1.** Prognostic factors and treatment parameters. SD: standard deviation; TUR-BT: transurethral resection of bladder tumor.

**Tabelle 1.** Prognosefaktoren und Therapiedaten. SD: Standardabweichung; TUR-BT: transurethrale Resektion des Blasenkarzinoms.

| Parameter   | Patients (n)      | Frequency (%) |
|---|-------------------|---------------|
| Sex   |                   |               |
| • Male  | 64                | 94            |
| • Female  | 4                 | 6             |
| Age   |                   |               |
| • Median  | 68 years          |               |
| • Range   | 42–82 years       |               |
| Clinical T-category                                 |                   |               |
| • T2  | 32                | 47            |
| • T3  | 20                | 29            |
| • T4  | 16                | 24            |
| Local disease status                                |                   |               |
| • Primary tumor                                     | 45                | 66            |
| • Locally recurrent tumor                           | 23                | 34            |
| Clinical nodal status                               |                   |               |
| • cN0   | 58                | 85            |
| • cN+   | 10                | 15            |
| Radicality of TUR-BT                                |                   |               |
| • R0  | 16                | 23            |
| • R1  | 12                | 18            |
| • R2  | 31                | 46            |
| • RX  | 9                 | 13            |
| Hydronephrosis                                      |                   |               |
| • None  | 52                | 76            |
| • Grade 1–2, no intervention                        | 1                 | 2             |
| • Unilateral percutaneous nephrostomy               | 11                | 16            |
| • Bilateral percutaneous nephrostomy                | 4                 | 6             |
| Total radiation dose                                |                   |               |
| • Median  | 55.7 Gy           |               |
| • Mean $\pm$ SD                                     | 55.7 $\pm$ 7.7 Gy |               |
| • Range   | 45.0–60.4 Gy      |               |
| Overall treatment time                              |                   |               |
| • Median  | 47 days           |               |
| • Range   | 21–70 days        |               |
| Type of simultaneous chemotherapy                   |                   |               |
| • None  | 7                 | 10            |
| • Cisplatin 25 mg/m <sup>2</sup> days 1–5 and 29–33 | 34                | 50            |
| • Paclitaxel twice weekly                           | 24                | 36            |
| • Combinations                                      | 3                 | 4             |

tolerance. The whole bladder received a boost up to 54 Gy in case of R0 resection or 59.4 Gy in case of non-radical TUR-BT (R1–2).

### Chemotherapy

Concurrent cisplatin-based chemotherapy was routinely used in all patients except in case of contraindications. The standard regimen was cisplatin 25 mg/m<sup>2</sup> per day on 5 consecutive days in the 1st and 5th week of radiotherapy (days 1–5 and 29–33) as published recently [17], and 34 patients (50%) were treated according to this regimen. Patients with impaired renal function were either treated with irradiation alone (n = 7) or received paclitaxel as alternative to cisplatin in a phase II protocol or on an individual decision (n = 27); the results of this study have been presented recently [3]. Patients with cisplatin chemotherapy had slightly lower creatinine serum levels prior to treatment than patients who did not received cisplatin (88.9  $\pm$  20.4  $\mu$ mol/l vs. 137.5  $\pm$  34.8  $\mu$ mol/l; p = 0.065).

### Restaging Cystoscopy with TUR-BT, Salvage Cystectomy

In general, restaging TUR-BT was considered part of the treatment concept as published earlier [17]. The objective of the restaging TUR-BT is, in general, to identify patients with residual tumor who are candidates for salvage cystectomy. In this analysis, only 46 patients underwent restaging TUR-BT, because the others were considered inoperable due to medical reasons and a consequence of the restaging TUR in terms of decision-making for further procedures was not expected (n = 19) or patients progressed clinically immediately after radiochemotherapy (n = 3).

### Statistical Methods

Patients were followed routinely in the urologic departments and once yearly in the department of radiotherapy. The median follow-up in survivors was 34 months (range 2–104 months). The analysis was performed with a standard statistical software (SPSS). Survival curves were compared with the log-rank test.

### Results

#### Completeness of TUR-BT and T-Category

16 patients (23%) had a microscopically complete TUR, and further twelve patients (18%) had an R1 resection. In 31 patients (46%) with extravesical extension, visible tumor was left after TUR-BT. The resection status was unknown or not further specified in nine patients (13%).

Resection status of TUR-BT was significantly correlated with T-category (Table 2). An R0 resection was achieved in 14/32 T2 tumors (44%) and 2/36 T3–4 tumors (6%). Macroscopically visible tumor was left in 22% of T2 tumors and 67% of T3–4 tumors.

#### Treatment Feasibility

55 patients (81%) completed treatment according to the prescribed schedule. In two patients (one with irradiation alone,

one with combined radiochemotherapy), radiotherapy was terminated earlier due to acute radiation enteritis. In eleven patients (16%), dose reductions of chemotherapy were necessary. In summary, the overall treatment compliance was good. The total dose was  $55.7 \pm 7.7$  Gy (range 45–60.4 Gy). The median overall treatment time was 47 days (range 21–70 days) and the mean weekly radiation dose  $8.6 \pm 1.3$  Gy.

### Response

Response was evaluated in 46 patients by cystoscopy and restaging TUR-BT. A histologically confirmed complete remission (CR) on restaging TUR-BT was observed in 40 patients (59% of all patients, 87% of patients who underwent restaging TUR-BT). CR rates were not significantly correlated to T-category (CR: 24/32 T2, 9/19 T3, and 9/16 T4 tumors) nor clinical nodal status (CR: 20/29 cN0, 4/10 cN+, 18/28 cNx), grading or number of preceding TURs. Patients with non-radical resection and macroscopic residual tumor (R2 resection) achieved a CR in only 39% (12/31); this figure was significantly lower as compared to patients with radical and microscopically complete (R0) TUR-BT (CR: 15/16, 94%;  $p = 0.013$ ). Furthermore, age and preexisting anemia had no impact on response.

### Acute Toxicity

Treatment was well tolerated in the majority of patients. Mild to moderate toxicity (grade 1–2) concerned bladder symptoms in 30% of patients and bowel symptoms in 28%. In 24 patients treated with paclitaxel, one mild allergic reaction occurred despite standard premedication. Other grade 1–2 toxicities included local skin reactions (40%), hematologic symptoms (29%), and nausea/vomiting (19%). Grade 3 toxicities in terms of cystitis occurred in 4% and severe diarrhea in 4% of the patients. Other grade 3 toxicities were not observed and no grade 4 toxicity occurred.

### Overall Survival

The overall survival of the whole group was 45% after 5 years. Survival according to clinical T-category was 62% for T2, 43% for T3, and 19% for T4 ( $p = 0.015$ ). For muscle-invasive cancers, a marked difference between tumors with invasion limited to the muscle wall (cT2) and extravesical spread (cT3–4) was noted (Figure 1). Age and pretreatment hemoglobin level had no significant impact on survival.

### Local and Systemic Control

In eleven patients, disease progression or relapse was observed. Ten patients developed a locoregional progression or recurrence (four of them with additional distant metastases) and received further treatment with palliative intent. Two of these patients received a second course of radiotherapy because of nodal recurrence. Systemic metastases ( $\pm$  local recurrence) occurred in nine patients (lung  $n = 1$ , bone  $n = 1$ , brain  $n = 2$ , multiple sites  $n = 5$ ).

**Table 2.** Significant association ( $p = 0.002$ , Pearson's  $\chi^2$ -test) between clinical T-category and radicality of transurethral resection in muscle-invasive tumors ( $T \geq 2$ ). Figures are numbers of patients in each category.

**Tabelle 2.** Signifikanter Zusammenhang ( $p = 0,002$ ,  $\chi^2$ -Test nach Pearson) zwischen klinischer T-Kategorie und Radikalität der transurethralen Resektion bei muskelinvasiven Tumoren ( $T \geq 2$ ). Angegeben sind die absoluten Patientenzahlen der jeweiligen Kategorie.

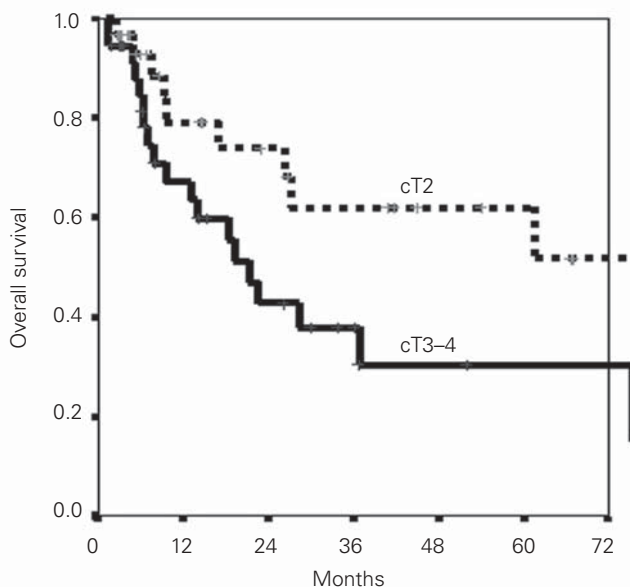
|     | R0 | R1 | R2 | RX |
|-----|----|----|----|----|
| cT2 | 14 | 8  | 7  | 3  |
| cT3 | 0  | 3  | 14 | 3  |
| cT4 | 2  | 1  | 10 | 3  |

### Bladder Preservation

So far, only one salvage cystectomy has been performed. All other patients with local relapse were treated with palliative intent at the time of local recurrence due to contraindications to radical surgery.

### Late Toxicities

With regard to the limited follow-up, data on long-term toxicities are not conclusive in this investigation. So far, the following long-term sequelae have been observed: reduced bladder capacity (5/47 evaluable patients), grade 1–2 chronic cystitis (4/64 patients), grade 1–2 mild enteritis (3/64 patients), one hydronephrosis due to fibrosis, one urethral stricture, and mild renal insufficiency after cisplatin chemotherapy in two



**Figure 1.** Significant impact of deep infiltration beyond the muscle wall (cT2 vs. cT3–4) on overall survival. Data of 70 patients with histologically proven muscle invasion ( $cT \geq 2$ ) are shown.

**Abbildung 1.** Signifikanter Einfluss der perivesikalen Infiltration (cT2 vs. cT3–4) auf das Gesamtüberleben. Dargestellt sind die Daten von 70 Patienten mit histologisch bestätigter Muskelinvasion ( $cT \geq 2$ ).

cases. None of these sequelae have required continuous medication or surgical intervention so far.

### Discussion

The efficacy of an organ-sparing approach including transurethral surgery, irradiation and simultaneous chemotherapy for locally advanced bladder cancer has been demonstrated in a variety of large prospective studies and population-based analyses [1, 2, 4, 5, 7–9, 11, 14–19, 21, 22, 24]. Although randomized trials are missing, the synopsis of the currently available data suggest that this multimodal approach does not compromise survival as compared to radical cystectomy and yields preservation of a functioning bladder in the vast majority of patients. The survival figures reported in these series are at least comparable, if not better than survival figures of the best contemporary European and US cystectomy series [14, 20]. Despite these promising results, however, organ-preserving treatment has not gained broad acceptance [6, 11, 15].

A minority of bladder cancer patients present with locally advanced inoperable disease or are no candidates for radical cystectomy due to age or comorbidity. This group of patients represents a negatively selected subgroup of muscle-invasive bladder cancer. However, these patients may be cured with definitive radiotherapy or radiochemotherapy. Shipley et al. achieved promising results in patients unsuitable for major surgery with a trimodality approach including transurethral surgery, radiotherapy, and concurrent chemotherapy [19].

Our data, in general, support those in the literature and further emphasize the high potential of radiochemotherapy for locally advanced bladder cancer, although the analysis in this paper has some limitations. Our patient group was relatively small and heterogeneous with regard to prognostic factors and was treated over a period of about 1 decade. This reflects the underlying referral strategies and must be taken into account when interpreting the data. The most striking difference as compared to other series with an organ-sparing approach is the fact that none of our patients received a salvage cystectomy, although salvage surgery was part of the treatment concept. This figure indirectly confirms the negative selection of patients.

The favorable outcome of patients with T3 and T4 tumors is remarkable with 5-year overall survival rates of 43% and 19%. These figures compare well to other series in the literature. The data suggest that the results of radiochemotherapy in locally advanced bladder cancer are robust and that patient selection has few impact, if any, on outcome.

Future clinical research issues concern, besides the optimization of the combined-modality treatment schedules, the identification of predictive factors. Retrospective analyses suggest that molecular markers such as apoptotic index or proliferation markers may help to identify patients who may benefit most from an organ-sparing approach [23].

### Conclusion

Our data support the use of an organ-preserving multimodality approach for muscle-invasive bladder cancer. TUR plus simultaneous radiochemotherapy plus selected salvage cystectomy is probably the optimal treatment for these patients, and the overall survival figures which have been reported in this and other investigations are robust and at least equal to current cystectomy series.

### Acknowledgment

All authors contributed significantly to the results and the manuscript. J. Dunst was the responsible radiation therapist, analyzed the results and wrote the manuscript. A. Diestelhorst performed the radiation treatment in the majority of patients and recorded the data. R. Kühn, H.-J. Scholz and P. Fornara performed the urologic treatment and follow-up. A.-C. Müller was responsible for some radiation treatments and assisted in the statistical analysis. The authors thank Mareike Kunze for skillful assistance in data management.

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**Address for Correspondence**

Professor Jürgen Dunst, MD  
UK-SH Strahlentherapie  
Ratzeburger Allee 160  
23538 Lübeck  
Germany  
Phone (+ 49/451) 500-6661, Fax -3324  
e-mail: juergen.dunst@strahlentherapie.uni-luebeck.de