Treatment Results of Radiation Therapy for Muscle-Invasive Bladder Cancer

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Purpose: To assess local control and survival rates in patients with muscle-invasive bladder cancer treated with external-beam radiotherapy and to investigate prognostic factors.

Patients and Methods: Between 1997 and 2007, 75 patients (male, n = 58; female, n = 17, median age, 74.2 years) with localized transitional cell carcinoma of the bladder (T2, n = 34; T3, n = 32; T4, n = 9) not suitable for radical surgery due to advanced age, comorbidity or inoperability underwent external-beam radiotherapy without simultaneous chemotherapy at the University Clinic of Therapeutic Radiology and Oncology, Medical University of Graz, Austria. A conformal four-field technique was used in all patients to treat the tumor and regional lymph nodes with single daily fractions of 1.8–2 Gy to a total dose of 50–50.4 Gy, followed by a cone-down to encompass the empty bladder which was boosted to 70–70.4 Gy. All patients had undergone transurethral tumor resection prior to radiotherapy which was macroscopically incomplete in 62 patients.

Results: Complete response was achieved in 65% of patients. Actuarial 3-year local control and metastases-free survival rates were 52.5% and 63.7%, 3-year local recurrence-free survival rate in complete responders was 71%. In univariate analysis, hydronephrosis, lymph vessel invasion, and macroscopic residual tumor were significantly predictive of disease progression. Hydronephrosis and lymph vessel invasion were also associated with a higher risk of local recurrence. The actuarial 3-year progression-free and overall survival rates were 40.1% and 56.9%, respectively.

Conclusion: Radiotherapy is an effective treatment option in terms of local control and survival even in elderly patients with locally advanced bladder cancer not suitable for cystectomy.

Key Words: Bladder cancer · External-beam radiotherapy · Local control · Organ preservation

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Stellenwert der primären Strahlentherapie von lokal fortgeschrittenen Blasenkarzinomen

Ziel: Analyse der Lokalkontroll- und Überlebensraten von Patienten mit muskelinvasiven Blasenkarzinomen nach perkutaner Strahlentherapie und Untersuchung von prognostischen Faktoren.

Patienten und Methodik: Zwischen 1997 und 2007 wurden 75 Patienten (Männer n = 58; Frauen n = 17; medianes Alter 74,2 Jahre) mit nichtmetastasiertem, muskelinvasivem Blasenkarzinom (T2 n = 34; T3 n = 32; T4 n = 9), bei welchen eine radikale Zystektomie aufgrund von Alter, Komorbidität oder inoperablem Tumor nicht durchführbar war, einer primären perkutanen Strahlentherapie an der Universitätsklinik für Strahlentherapie und Radioonkologie Graz, Österreich, unterzogen. Keiner der eingeschlossenen Patienten erhielt eine simultane Chemotherapie. Der Primärtumor und der pelvine Lymphabfluss wurden in einer Vier-Felder-Technik mit 50–50,4 Gy (1,8–2 Gy/d) bestrahlt, die Harnblase wurde auf 70–70,4 Gy aufgesättigt. Bei allen Patienten wurde vor der Strahlenbehandlung eine transurethrale Resektion durchgeführt, bei 62 Patienten erfolgte die Strahlentherapie nach makroskopisch inkompletter Tumorresektion.

Ergebnisse: Eine komplette Remission wurde bei 65% der Patienten beobachtet. Die aktuarische 3-Jahres-Lokalkontrollrate und metastasenfreie Überlebensrate betrugen 52,5% und 63,7%, bei Patienten mit klinisch kompletter Remission lag die lokalrezidivfreie 3-Jahres-Überlebensrate bei 71%. In der univariaten Analyse waren Hydronephrose, Lymphgefäßinvasion und makroskopischer Tumorrest signifikant mit Tumorprogression assoziiert. Weiters zeigte sich eine signifikante Assoziation zwischen Hydronephrose, Lymphgefäßinvasion und dem Auftreten eines Lokalrezidivs. Das aktuarische progressionsfreie 3-Jahres-Überleben und Gesamtüberleben betrugen 40,1% und 56,9%.

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Schlussfolgerung: Die primäre perkutane Bestrahlung stellt eine effektive Behandlungsoption in Bezug auf die lokale Kontrolle und das Überleben bei Patienten auch fortgeschrittenen Alters mit lokal fortgeschrittenem Blasenkarzinom dar, die für eine radikale Zystektomie nicht geeignet sind.

Schlüsselwörter: Blasenkarzinom · Primäre perkutane Strahlentherapie · Lokale Kontrolle · Organerhalt

Introduction

In Europe and in the USA, bladder cancer is the fourth most common cancer in men and the eighth most common malignancy in women [22]. At the time of diagnosis, 20% of patients present with muscle-invasive tumors, and without treatment > 85% of patients with invasive disease succumb to their disease within 2 years after diagnosis [49]. The standard therapy for patients with muscle-invasive cancer in most institutions is still radical cystectomy and pelvic lymphadenectomy providing 5-year overall survival rates of 60% [47, 49].

New surgical techniques emerged rapidly during the last years with the development of continent orthotopic urinary diversion and nerve-sparing techniques to improve both functional results and quality of life [3, 4, 18], but even the construction of a neobladder cannot substitute for the original urinary bladder.

Bladder-preserving strategies such as radiotherapy and radiochemotherapy combined with a transurethral resection of the bladder tumor (TURBT) have been shown to offer an attractive alternative to radical cystectomy providing complete response rates of 60–85%, 5-year survival rates of 50–60%, and survival rates with an intact bladder of 40–45% [24, 25, 34, 35, 40, 51]. Although there are no randomized trials comparing radical cystectomy with bladder-preserving therapy, long-term data show that overall and disease-specific survival rates in radical cystectomy series of patients with T2–T4a tumors are comparable to those achieved by bladder-preserving strategies [7, 14, 27, 28].

Radiotherapy is often limited to patients who are medically unfit and/or who are considered unresectable representing a negatively selected subgroup. Although the treatment results are inferior to better selected patients, radiotherapy has been shown to offer long-term tumor control and survival even in this high-risk population [13, 35].

The aim of the present investigation was to retrospectively analyze the treatment results of radiotherapy for locally advanced bladder cancer in patients not suitable for cystectomy and to evaluate prognostic factors.

Patients and Methods

The cohort was comprised of 75 patients (female, n = 17; male, n = 58) with histologically confirmed, muscle-invasive transitional cell carcinoma of the bladder who received external-beam irradiation at the University Clinic of Therapeutic Radiology and Oncology, Medical University of Graz, Austria, between 1997 and 2007.

The included patients had inoperable T4b tumors or were medically unfit for radical surgery due to age and reduced performance status and/or comorbidities. There was no cutoff age for the patients to be treated either surgically or by radiotherapy. The Eastern Cooperative Oncology Group (ECOG) or Karnofsky Score as well as the American Society of Anesthesiologists (ASA) and Goldman scoring systems were applied to objectivize the performance status and to predict the operative risk.

Median age at initiation of radiotherapy was 74.2 years (mean, 72.7 years; range, 47.7–90.6 years). Tumor stages were classified according to the 2002 guidelines of the International Union Against Cancer (UICC). Staging procedures included clinical examination, chest X-ray, pelvic and abdominal computed tomography (CT) scan, and cystoscopy. Furthermore, all patients had undergone TURBT prior to radiotherapy and 46 patients (61%) had a history of at least two TURBTs. 13 patients were treated after microscopically incomplete resection, whereas 62 patients received radiotherapy for a macroscopic residual tumor. Intravesical chemo- or immunotherapy was administered to seven patients (9%) prior to radiation treatment. No patient had evidence of distant metastases at the onset of radiation therapy. Details on tumor characteristics are given in Table 1.

Radiation Treatment

External-beam radiation with 18 MV photons was used to encompass the tumor and the pelvic lymph nodes in a four-field-box technique to 50–50.4 Gy, then a cone-down was applied to boost the bladder to 70–70.4 Gy with an anterior and two lateral fields. All fields were treated daily, 5 days/week. Daily fraction sizes ranged from 1.8 to 2 Gy. Patients were instructed to have an empty bladder during the CT-based planning procedure and during irradiation. Individually manufactured, focused cerrobend blocks were used to shield the surrounding tissues and were replaced in 1998 by three-dimensional conformal treatment planning and the use of multileaf collimators. None of the included patients received simultaneous chemotherapy.

Acute and late genitourinary and gastrointestinal toxicity was graded according to standard Radiation Therapy Oncology Group (RTOG) criteria.

Statistical Analysis

All time-dependent event rates and median time to event were estimated by the Kaplan-Meier method. Confidence intervals (CIs) of survival rates were calculated symmetrically on the log-hazard scale. Median time of follow-up was calculated with time to last follow-up as event and time to death as censoring time (inverse Kaplan-Meier method). All

Table 1. Tumor characteristics. RT: radiotherapy; Tis: carcinoma in situ.
Tabelle 1. Tumorcharakteristika. RT: Radiotherapie; Tis: Carcinoma in situ.

Characteristics	Patients n (%)
Tumor stage	
• T2	34 (45)
• T3	32 (43)
• T4	9 (12)
Histological grade	
• G2	8 (11)
• G3	60 (80)
• G4	7 (9)
Clinical lymph node involvement	
• N0	62 (83)
• N1	6 (8)
• N2	7 (9)
Transurethral resections prior to RT	
• One	29 (39)
• Two	31 (41)
• More than two	15 (20)
Margin status	
• R1	13 (17)
• R2	62 (83)
Multifocality	
• Yes	6 (8)
• No	69 (92)
Associated Tis	
• Yes	6 (8)
• No	69 (92)
Lymph vessel invasion	
• Yes	20 (27)
• No	55 (73)
Hydronephrosis	
• Yes	24 (32)
• No	51 (68)

time intervals were calculated from the end of radiotherapy. Local control was defined as the absence of local bladder failure, local recurrence-free survival as the time interval from the end of radiation treatment to bladder recurrence, local progression-free survival as the time interval from the end of radiation treatment to bladder recurrence or bladder tumor progression, progression-free survival as the time interval from the end of radiation treatment to locoregional and/or distant failure, and distant metastases-free survival as the interval from the end of radiotherapy to distant disease progression.

The influence of prognostic factors on event rates was assessed by a univariate Cox model, using the score criterion for testing. The calculations were performed with the package survival2.35-4 of R 2.8.1 (*http://www.r-project.org*). p-values < 0.05 were considered statistically significant.

Follow-Up

3 months after completion of radiotherapy, a cystoscopy was performed. The disappearance of all signs of cancer in response to treatment was defined as complete response. A re-TURB to distinguish between complete responders and noncomplete responders was not demanded in the present series, as the included patients were not considered to be suitable for further treatment options such as salvage cystectomy. Patients were followed by their urologist and radiation oncologist every 3 months in years 1–3, every 6 months for the next 2 years, and annually thereafter. Follow-up examinations included toxicity evaluation, physical examination, routine laboratory parameters, cystoscopy, abdominal/pelvic CT, and chest X-ray. Isotope bone scans were arranged, if clinically indicated.

Results

The median time of follow-up was 29.4 months. In 49 patients (65%), a complete response was observed, and 22% of these patients (11/49) developed a local recurrence. In 65% of patients (17/26) with initial incomplete response, local disease progression was observed during follow-up time. Distant metastases were found in 31% of patients (23/75; bone, n = 8; extrapelvic lymph nodes, n = 10; lung, n = 4; brain, n = 3; liver, n = 6; other sites, n = 4); 15% of patients (11/75) experienced both, local and distant failure. Only one local recurrence was superficial and successfully treated by TURBT, whereas in the remaining patients, local recurrences were muscle-invasive. In case of muscle-invasive progression or distant metastasis, patients received palliative care including palliative TURBT in five patients.

Overall actuarial 3-year local progression-free and metastases-free survival rates were 52.5% (95% CI 37.3–65.7%) and 63.7% (95% CI 49.0–75.2%), respectively. The actuarial 3-year local recurrence-free survival in patients with complete response after radiotherapy was 71% (95% CI 50.6–84.5%). 37% of patients (28/75) died; 35% of patients (26/75) due to tumor progression. The actuarial 3-year progression-free and overall survival rates were 40.1% (95% CI 27.2–52.7%) and 56.9% (95% CI 42.4–69.1%), respectively.

The following patient and disease characteristics were analyzed for their prognostic impact: tumor stage, histological grading, residual tumor burden, lymph node and lymph vessel involvement, associated carcinoma in situ (Tis), multiple recurrences, multifocality, and hydronephrosis.

Univariate analysis revealed that hydronephrosis, lymph vessel invasion and macroscopic residual tumor burden were statistically significant predictive factors of disease progression (Table 2). 20% of patients (4/20) with lymph vessel invasion, 25% of patients (6/24) with hydronephrosis and 42% of patients (26/62) with R2 resection had no evidence of disease progression (local and/or distant). Furthermore, hydronephrosis and lymph vessel invasion were associated with higher risk of local recurrence whereas macroscopically incomplete tumor resection was not significant (Table 3). 41% of patients (10/24) with hydronephrosis and 25% of patients (5/20) with

Table 2. Univariate analysis of prognostic factors for disease progression. CI: confidence interval; Tis: carcinoma in situ.

Tabelle 2. Univariate Analyse von prognostischen Faktoren bezüglich Tumorprogression. CI: Konfidenzintervall; Tis: Carcinoma in situ.

Prognostic factors		Relative risk	95% CI	p-value
Tumor stage	T2	1.00		0.583
	T3	1.30	(0.69;2.6)	0.38
	T4	0.90	(0.3;2.4)	0.83
Tumor grade	G2	1.00		
	G3–4	1.64	(0.58;4.7)	0.35
Lymph node involvement	No	1.00		
	Yes	1.40	(0.68;2.87)	0.36
Lymph vessel invasion	No	1.00		
	Yes	2.57	(1.34;4.9)	0.00316
Macroscopic residual tumor	No	1.00		
	Yes	3.36	(1.17;9.6)	0.02
Multiple recurrences	No	1.00		
	Yes	1.32	(0.68;2.5)	0.418
Multifocality	No	1.00		
	Yes	1.06	(0.33;3.5)	0.92
Associated Tis	No	1.00		
	Yes	0.76	(0.23;2.5)	0.64
Hydronephrosis	No	1.00		
	Yes	2.64	(1.4;5)	0.0019

Table 3. Univariate analysis of prognostic factors for local recurrence. CI: confidence interval; Tis: carcinoma in situ.

Tabelle 3. Univariate Analyse von prognostischen Faktoren bezüglich Lokalrezidivrisiko. CI: Konfidenzintervall; Tis: Carcinoma in situ.

Prognostic factors		Relative risk	95% CI	p-value
Tumor stage	T2	1.00		0.583
	T3	1.40	(0.63;3)	0.42
	T4	0.70	(0.2;2.6)	0.62
Tumor grade	G2	1.00		
	G3–4	1.07	(0.36;3.1)	0.907
Lymph node involvement	No	1.00		
	Yes	1.44	(0.61;3.4)	0.41
Lymph vessel invasion	No	1.00		
	Yes	2.96	(1.36;6.4)	0.00417
Macroscopic residual tumor	No	1.00		
	Yes	2.86	(0.85;9.6)	0.076
Multiple recurrences	No	1.00		
	Yes	1.89	(0.82;4.3)	0.129
Multifocality	No	1.00		
	Yes	1.58	(0.47;5.3)	0.453
Associated Tis	No	1.00		
	Yes	0.74	(0.17;3.1)	0.68
Hydronephrosis	No	1.00		
	Yes	3.12	(1.48;6.6)	0.0017

Table 4. Incidence of treatment-related side effects.

Tabelle 4. Inzidenz therapiebedingter Nebenwirkungen.

	Acute side effects n (%)				
	0	**1**	**2**	**3**	**4**
All	16 (21)	34 (45)	20 (27)	5 (7)	0
Bladder	25 (33)	29 (39)	16 (21)	5 (7)	0
Bowel	42 (56)	18 (24)	15 (20)	0	0
	Late side effects n (%)				
	0	**1**	**2**	**3**	**4**
All	40 (53)	18 (24)	8 (11)	9 (12)	0
Bladder	47 (63)	15 (20)	7 (9)	6 (8)	0
Bowel	64 (85)	6 (8)	2 (3)	3 (4)	0

lymph vessel invasion were controlled locally. None of the investigated parameters was a significant predictor of overall survival or distant metastases.

All patients were assessed for acute radiation-induced toxicity, 50 patients were assessed for late toxicity after 1 year and 19 patients after 3 years. Acute gastrointestinal (n = 15) and/or genitourinary toxicity (n = 21) ≥ grade 2 was found in 33% of patients (25/75).

In 37% of patients, late radiation-induced bladder toxicity RTOG ≥ 1 was observed, and 17% of patients (13/75) experienced late genitourinary side effects ≥ grade 2. In 15% of patients (11/75), late radiation-induced gastrointestinal toxicity RTOG ≥ 1 was found, and 7% of patients (5/75) experienced late gastrointestinal side effects ≥ grade 2 (Table 4). Eleven patients were followed for > 5 years and three of them (27%) had developed radiation-induced late toxicity grade 3.

Three patients developed a stenosis of the sigmoid colon requiring surgical intervention. In 19% of patients (14/75), placement of a nephrostoma was necessary; in two patients for hydronephrosis due to fibrosis, and in twelve patients because of local recurrence. Information on bladder function was available in 13 patients. After a median follow-up time of 4 years (mean, 4.15 years; 95% CI 2.9–5.4 years) bladder capacity was < 100 ml in one patient, 100–200 ml in two, 200–300 ml in two, and > 300 ml in eight patients.

Discussion

The standard of care for localized transitional cell carcinoma of the bladder with invasion to the muscularis propria is radical cystectomy. Currently, data from randomized trials comparing cystectomy with bladder-conserving therapy are not available, but in a Cochrane analysis by Shelley et al., an overall survival benefit has been demonstrated with radical surgery, however, it has to be considered that only three trials were included for analysis [44].

By advances in perioperative management, cystectomy has been shown to be suitable and to result in acceptable outcome in terms of qualitiy of life and survival even in elderly patients [23, 46] despite a higher risk of perioperative mortal-

ity and morbidity compared to younger patients that makes careful surveillance and patient selection necessary [15]. However, a subset of patients present with inoperable tumors or are unfit for radical surgery due to serious comorbidity or advanced age associated with reduced preformance status and high operative risk. These patients are commonly referred to local radiotherapy, and even in this negatively selected group external-beam radiotherapy has been shown to be feasible and effective providing local control rates ranging from 50% to 65% and overall survival rates ranging from 36% to 69% at 3 years [13, 17, 27, 30, 35, 36].

Currently, efforts are ongoing to optimize irradiation techniques and fractionation regimens to further improve tumor control and survival [11, 12, 37, 45, 54]. Results of previous studies suggested that hyperfractionated and accelerated regimens might be superior to conventional fractionation techniques [17, 33, 48]. More recently, however, it has been hypothesized that the differences in the outcome between different radiation schedules might be more related to the total dose than to the fractionation regimen [40]. In the present series, conventionally fractionated radiotherapy provided complete local tumor remission in 65% of patients leading to a 3-year local control rate of 53% and has been found to be feasible even in elderly patients. These data compare favorably with those recently published by Piet et al. who reported a 3-year local control rate of 56% in patients using an accelerated regimen [35].

In several phase II studies and one phase III study, concomitant radiochemotherapy has been reported to increase the rate of complete responders as compared to radiotherapy alone leading to a significantly improved overall survival [31, 34, 40–42]. The only prospective, randomized comparison of radiotherapy alone versus concomitant chemoradiation in bladder cancer demonstrated an improved local control rate when cisplatin was given in combination with radiotherapy [9]. Cisplatin-based chemotherapy was not administered in the patients who were included in the present analysis because of contraindications such as renal dysfunction, peripheral neuropathy, cerebrovascular or cardiovascular disease, hearing disorder, hematologic disease, or infections.

It has to be taken into account that most studies on chemoradiation included patients who were able to receive a platinum-based chemotherapy and to undergo surgery in case of persistent disease after initial chemoradiation making the comparison with the negatively selected patient group in the present study difficult. More recently, hypoxic cell sensitizers and inhibitors of the epidermal growth factor receptor have been shown to increase radiosensitivity in bladder cancer [8, 20]. Combinations of radiotherapy with these novel radiosensitizing agents might provide future improvements in tumor control and survival, especially for patients with medical comorbidities which preclude chemotherapy.

Findings of previous studies indicated that hydronephrosis and incomplete TURBT might be inversely associated with tumor control [2, 7, 43]. Similar results have been obtained in the present series, however, associations between tumor stage, grade, associated Tis, and local tumor control could not been found. The high frequency of macroscopically incomplete tumor resections might also have strongly contributed to inferior tumor control and survival rates compared to those achieved with novel chemoradiation regimens. Currently, the prediction of radiation response is limited to the use of traditional factors such as tumor stage, completeness of TURBT, absence of hydronephrosis, and pelvic lymph node involvement. Recently, the index of apoptotic tumor cells and the expression of regulators of apoptosis and proliferation markers have been reported to be associated with local tumor control [6, 39, 52, 53], and it might be helpful to have additional molecular markers to aid in predicting clinical response and to identify patients who will benefit most from radiotherapy or combined radiochemotherapy.

Definitive radiotherapy for bladder cancer has its merits but can be associated with several side effects. Acute radiation-induced adverse effects such as urocystitis and enteritis occur commonly but can be easily managed by symptomatic treatment. In the present series, 79% of patients developed acute gastrointestinal or genitourinary symptoms that resolved within 3 week after completion of radiotherapy. Patients with a history of multiple transurethral resections prior to radiotherapy have been suggested to be predisposed to develop acute radiation cystitis, and are also at higher risk to suffer from bladder shrinkage thereafter [38]. A limitation of the present investigation is that information on bladder capacity is available in only 13 patients that makes a comparison with other treatment modalities difficult. Late bladder toxicity has been reported to occur predominately if radiation doses > 65 Gy are administered to large areas of the bladder. Compared to chemoradiation regimens that commonly utilize total doses of ≤ 60 Gy, a higher frequency of late sequelae was observed in the current analysis. 37% of patients developed late bladder toxicity RTOG ≥ 1 and 8% suffered from late side effects grade 3 including severe urgency and dysuria or frequent macroscopic hematuria. The high frequency of late side effects has to be related to the relatively high dose of 70 Gy delivered to the entire bladder that makes it essential to reduce the total dose to the bladder. To avoid an impairment of tumor control, combinations with radiosensitzing agents will be helpful.

Furthermore, it could be considered to reduce the bladder treatment volume by selectively boosting the tumor-carrying bladder tissue. Previous results indicated that in patients with solitary bladder tumors, reduction of the high dose volume to the bladder tumor area does not impair treatment efficacy [5, 19, 50]. Interesting new approaches being explored include the use of partial-bladder radiotherapy, brachytherapy, and proton therapy [5, 10, 19, 21, 37, 50]. Additionally, refinements in the techniques of radiation delivery such as image-guided and intensity-modulated radiotherapy may allow dose escalation to further improve tumor response and long-term tumor control [1, 16, 21, 26, 29, 32, 45].

Conclusion

The current data show that external radiotherapy is effective in achieving tumor control in patients with locally advanced bladder cancer not suitable for radical cystectomy and it was found to be feasible even in elderly patients. In agreement with previous reports, hydronephrosis, macroscopically incomplete tumor resection and lymph vessel invasion were found to be associated with disease progression. To minimize radiation toxicity, it will be necessary to reduce the total dose to the bladder and/or to reduce the high dose volume to the bladder tumor area. Further future efforts should be directed to identifying molecular markers predictive of radiation response to enable a selection of patients with a high risk of recurrence.

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