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Treatment Outcome and Prognostic Variables for Local Control and Survival in Patients Receiving Radical Radiotherapy for Urinary Bladder Cancer

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The aim of this retrospective study was to analyze the outcome of radical radiotherapy in 292 patients with bladder cancer and to identify prognostic factors for local control and survival. Median age was 72.3 years (range 45–83 years). Median follow up was 66 months (range 18–121 months). All patients were treated by use of a standard 3-field technique with 60 Gy in 30 fractions to the tumor and the bladder. The elective lymph nodes were treated with doses in the range from 46 Gy to 60 Gy. Complete response was obtained in 52% of the patients at 3-month control. However, 41% of all patients with an initial CR developed recurrence during follow-up. The 3-year and 5-year overall survival rate was 31% and 21%, respectively. Performance status, T-stage, macroscopic complete TURB, hydronephrosis, and serum creatinine were independent prognostic factors for overall survival and, thus, important for the selection of patients for curative intended radiotherapy. During radiotherapy acute transient side effects were recorded in 78% of the patients; severe bowel complications were recorded in 9 patients (3%). Following radiotherapy, 10 patients (3%) developed intestinal reactions requiring surgery. Three patients (1%) were cystectomized because of severe radiation reactions in the bladder. At 5-year follow-up, the actuarial risk of complications requiring surgery was 15%. Treatment-related mortality was 2%.

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In Denmark as in many other countries, radical radiotherapy is regarded as inferior to cystectomy of muscle-invasive bladder cancer (1). As a consequence, only patients who are considered unfit for surgery or who refuse cystectomy are offered radical radiotherapy. The survival following radical radiotherapy depends on several factors. One important factor is the selection procedure of patients for radiotherapy (2). The best results have been reported in studies in which radiotherapy is considered the first treatment of choice. In these studies, 5-year overall survival rates ranging between 24% and 50% have been reported (3–11). These results are contrary to studies in which patients have been selected for radiotherapy after being judged unsuitable for cystectomy due to age and/or medical comorbidity. In such studies with a negative selection of patients for radiotherapy, 5-year overall survival rates ranging between 18% and 31% have been reported (12–18).

The purpose of this retrospective study was to investigate local control, survival, and morbidity in a Danish patient population, negatively selected for radical radiotherapy for urinary bladder cancer. Furthermore, we wanted to investigate a variety of factors of importance for local control and survival.

MATERIAL AND METHODS

In the period 1994 to 2002, a total of 295 consecutive patients received primary radical radiotherapy for bladder cancer in the Department of Oncology, Aarhus University Hospital.

Since CT dose planning was introduced in the department in 1994, this period was chosen to establish homogeneity in the treatment technique and dosage. All patients were offered radiotherapy with a curative intent after been judged unfit for cystectomy. The patients had at least one TURB at the referring department of urology. Medical records including a description of the staging cystoscopy and biopsies were reviewed retrospectively. Information concerning medical history, last TURB, pretreatment blood tests, ultrasound examination or diagnostic CT scan of the abdomen, and chest x-ray was recorded. Staging was performed in accordance with the 1978 UICC TNM classification (19). Grading of the tumor was performed in accordance with Bergkvist (20).

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Follow-up during and immediately after radiotherapy took place at the department of oncology. Subsequent follow-up took place at the referring department of urology with a cystoscopy 3–4 months after radiotherapy and then regularly at 3- to 6-month intervals. Complete response was defined as no tumor at cystoscopy, but did not in all cases include histological confirmation of the result.

Follow-up information was collected from medical records. In case of missing information, contact was established with the general practitioner as well as other hospitals.

The following factors were included for analysis. Patient-related factors: age, gender, WHO performance status (21). Tumor-related factors: clinical T-stage analyzed in each stage and categorized as bladder-confined tumors (T1–T3a) vs. tumors reaching beyond the bladder (T3b–T4ab), N-stage, histology categorized as pure transitional carcinomas vs. squamous-cell carcinomas and mixtures, CIS, multiplicity, Bergkvist grade, hydronephrosis, blood tests, and complete response. Treatment-related factors: TURB categorized as macroscopic complete vs. not complete, and radiation time prolongation. The factors analyzed are summarized in Tables 1 and 2.

Radiotherapy

All patients received CT-based radiotherapy positioned in the supine position. The standard technique consisted of a three-field technique allowing an individual field shaping with multi-leaf collimators or lead blocks, and individually optimized field weights, plus wedges as well as compensation filters. The tumor and the bladder were treated with a 2 cm geometric margin with 60 Gy in 2 Gy fractions, 5 fractions/week with 6–20 MV photons. All patients with advanced stage, i.e. T4b and/or node-positive disease, treated in the period from 1994 to 1999 were also prescribed 60 Gy to the external and internal iliac lymph nodes. The remaining patients were prescribed 46 Gy to the external and internal iliac lymph nodes. All doses were specified according to the ICRU-50 allowing a dose variation of $\pm 5\%$ to be accepted in the Planning Target Volume (22).

Statistics

The two main endpoints were local control and overall survival measured from the start of radiotherapy. With regard to local control, patients were classified as failures on the date persistent tumor or local recurrence was diagnosed. Patients who relapsed distantly without local recurrence were censored on the day of diagnosis. Patients without

Table 1

Distribution of patients and actuarial 3-year and 5-year local control and overall survival rates according to treatment-related and patient-related factors (percentages may not reach 100% due to missing values)

Factor	%	Local control[1]			%	Overall survival		
		3 year (95% C.I.)	5 year (95% C.I.)	p[2]		3 year (95% C.I.)	5 year (95% C.I.)	p[2]
All patients	100	42 (36–49)	37 (30–45)	N[3]	100	31 (26–37)	21 (16–27)	N[3]
Age category								
45–59	7	38 (16–59)	38 (16–59)	0.19	8	21 (7–40)	21 (7–40)	0.62
60–64	14	30 (15–48)	25 (11–43)		13	19 (8–33)	16 (6–29)	
65–69	17	33 (18–49)	28 (13–45)		17	32 (20–46)	14 (5–30)	
70–74	34	50 (37–59)	45 (32–57)		34	33 (24–42)	25 (15–35)	
75–84	28	48 (35–60)	36 (15–57)		31	36 (25–47)	20 (9–34)	
Gender								
Male	80	44 (37–52)	38 (29–47)	0.11	81	32 (25–38)	20 (14–26)	0.45
Female	20	34 (22–48)	35 (22–48)		19	27 (16–40)	25 (14–37)	
PS								
0–1	94	44 (37–51)	39 (31–47)	0.01	90	34 (28–40)	22 (17–29)	<0.01
≥2	6	0	0		10	4 (0–15)	4 (0–15)	
TURB								
Complete	30	69 (53–59)	55 (39–69)	<0.01	28	55 (43–65)	37 (24–50)	<0.01
Incomplete	69	30 (23–38)	30 (23–38)		71	21 (16–28)	14 (9–20)	
Duration								
36–42 days	73	44 (36–52)	39 (30–47)	0.56	72	32 (26–39)	21 (15–28)	0.48
42–53 Days	27	38 (25–50)	34 (21–48)		28	31 (24–41)	22 (13–34)	

[1]38 patients were never evaluated.
[2]Log rank test.
[3]Not relevant.

Table 2

Distribution of patients and actuarial 3-year and 5-year local control and overall survival rates according to tumor-related factors (percentages may not reach 100% due to missing values)

Factor	%	Local control[1]			%	Overall survival		
		3 year (95% C.I.)	5 year (95% C.I.)	p[2]		3 year (95% C.I.)	5 year (95% C.I.)	p[2]
T-stage								
T1	2	100	100	<0.01	2	100	100	<0.01
T2	24	61 (46–73)	54 (35–70)		22	51 (38–63)	30 (16–46)	
T3a	28	60 (47–71)	48 (31–63)		28	40 (28–50)	29 (17–42)	
T3b	30	22 (12–34)	22 (12–34)		31	17 (10–27)	13 (7–22)	
T4a	10	21 (8–40)	21 (8–40)		11	11 (13–26)	0	
T4b	6	0	0		7	5 (0–21)	0	
N-stage								
N0	4	70 (33–89)	58 (23–82)	0.07	3	60 (25–83)	60 (25–83)	0.02
N1	11	28 (13–45)	28 (13–45)		10	31 (15–48)	22 (8–39)	
N2	4	16 (1–50)	0		4	18 (3–44)	0	
Nx	82	44 (36–51)	40 (31–49)		83	31 (25–37)	20 (15–27)	
Histology								
Pure	85	44 (37–51)	41(33–48)	0.03	85	32 (26–38)	22 (17–29)	0.07
Mixed	15	22 (8–42)	22 (8–42)		15	22 (10–36)	15 (4–32)	
Grade[3]								
2	5	30 (7–58)	30 (7–58)	0.68	5	30 (8–57)	20 (3–47)	0.35
3	73	44 (36–52)	38 (29–49)		71	35 (28–43)	23 (16–31)	
4	22	48 (30–65)	43 (24–61)		24	25 (15–37)	19 (10–32)	
CIS								
Yes	25	41 (27–55)	29 (13–47)	0.81	24	28 (17–39)	17 (8–29)	0.76
No	54	39 (30–48)	35 (25–45)		54	31 (24–39)	21 (14–29)	
Multiplicity								
Yes	14	49 (31–65)	49 (31–65)	0.24	15	25 (13–40)	16 (6–30)	0.85
No	82	40 (33–47)	35 (26–43)		82	30 (24–36)	20 (15–27)	
HGB[4]								
Normal	50	47 (38–56)	42 (32–52)	0.05	48	39 (31–47)	29 (21–38)	<0.01
Low	50	37 (27–46)	31 (18–44)		52	33 (16–31)	11 (5–20)	
Creatinine[4]								
Normal	81	45 (38–52)	41 (33–49)	0.03	78	34 (28–40)	26 (20–33)	<0.01
High	19	34 (21–48)	15 (2–42)		22	21 (12–32)	0	
LDH[4]								
Normal	83	40 (33–48)	35 (28–43)	0.27	82	34 (28–40)	23 (17–29)	0.02
High	7	60 (34–78)	60 (34–78)		8	9 (2–25)	9 (2–15)	
AP[4]								
Normal	86	41 (34–48)	36 (28–43)	0.65	84	33 (27–39)	22 (16–28)	0.02
High	7	49 (23–71)	49 (34–78)		8	7 (1–26)	7 (1–26)	
Hydrourether								
No	60	49 (40–56)	42 (28–44)	0.05	57	39 (32–47)	8 (20–36)	<0.01
Yes	40	33 (23–43)	33 (23–71)		43	20 (13–28)	12 (5–20)	

[1]38 patients were never evaluated.
[2]Log rank test.
[3]Only pure transitional cell carcinomas.
[4]Haemoglobin: low (male) <8.4 mmol/l (13.44 g/dl), low (female) <7.4 mmol/l (11.84 g/dl); creatinine: normal <120 μm/L. AP; low (<70years) <270 U/L, low (>70 years) <400 U/L; LDH: low <500 U/L, high >500 U/L.

evidence of local recurrent cancer were censored at the last follow-up, or if alive, at the time of analysis. Patients not evaluated with a cystoscopy 3–4 months after radiotherapy were registered as non-evaluable for the analysis of local control, but not for the analysis of survival.

Life-table calculations were done using the Kaplan–Meier method. Comparison between the curves was done using the log-rank test. Variables with p-values less than 0.10 were included in a multivariate analysis. A stepwise procedure using proportional hazard regression analysis

was used to identify factors of importance with regard to local control and survival (23). The selection of covariates was obtained by the use of stepwise regression using the maximum likelihood ratio test with forward and backward elimination procedures. At each step, the assumption of proportional hazards was tested with the use of log-cumulative hazard plots, adjusted for the other variables as covariates in the model. The significance of difference between proportions was determined using Fisher's exact test (2-tailed). Statistical analyses were performed using STATA 8 software package (StataCorp. 2003 Stata statistical software: Release 8.0. College Station, TX: Stata Corporation).

RESULTS

A total of 295 patients received radical radiotherapy for urinary bladder cancer in the period from 1994 to 2002. In three patients, hospital records were missing. Thus, 292 patients (236 males and 56 females) with a median age of 72.3 years (range 45–83 years) were included in the study. Patient characteristics are shown in Tables 1 and 2.

Staging procedures before radiotherapy

A total of 21% of all patients had a history of a previous bladder tumor; the remaining 79% were treated for a newly diagnosed bladder tumor. At least one TURB including a bimanual examination was performed in all patients. TURB was reported to be macroscopically complete in 21% of the patients and incomplete in 79% of the patients. In 3 patients, this information was not recorded. Histological assessment of regional lymph nodes was performed in 17% of patients. All but one patient had intravenous pyelography. Ultrasound examination of the abdominal cavity was performed in 52% of patients, while 48% of patients had a diagnostic CT scan. Chest x-ray was performed in 93% of patients, while 7% of patients had a CT scan of the chest. Bone scan was only performed on specific indications (5% of patients). Pretreatment serum hemoglobin and serum creatinine was available in all patients, whereas the liver enzymes, alkaline phosphate (AP), lactate dehydrogenase (LDH), alanine aminotransferase (ALAT) were available in only 84% of patients (see Table 2).

Tumor characteristics

Tumor characteristics are summarized in Table 2. In all, 98% of patients had muscle-invasive bladder cancer. Some 85% of the patients had pure transitional tumors, predominantly Bergkvist grade 3. The remaining 15% had mixed tumors (13%) or pure squamous-cell carcinomas (2%). Carcinoma in situ and multiplicity was found in 24% and 15% of patients, respectively. In 21% of patients, information concerning carcinoma in situ was missing, as selected biopsies were not performed.

Radiotherapy

In 30% of patients, 60 Gy were prescribed to the internal and external iliac lymph nodes; the remaining 70% of patients were treated with 46 Gy to the local lymph nodes. Significantly more patients with advanced T-stage ($\chi^2 = 40.46$, $p < 0.001$) as well as N-stage ($\chi^2 = 79.67$, $p < 0.001$) were treated with 60 Gy as compared with 46 Gy, to the internal and external iliac lymph nodes. Treatment time was planned to 42 days. In 28% of the patients, overall treatment time ranged from 43 to 54 days. Prolongation was caused by acute toxicity in 7% of patients, and holidays or machine breakdown caused the delay in the remaining 21% of patients. Only 2% of patients had more than a one-week treatment time prolongation.

Outcome of radiotherapy

At time of analysis, median follow-up time was 66 months (range 18–121 months). In total, 74% of all patients were dead. Of the living patients, 85% were without evidence of disease, whereas 15% had recurrent bladder cancer.

The results of radiotherapy in terms of complete response and local control rates are illustrated in Fig. 1. A complete response 3–4 months following radiotherapy was recorded in 152 patients (52%). A complete response was independently related to overall survival ($p < 0.01$) with a three-year survival rate of 54% (95% CI. 46–62%) in patients with a complete response, and a three-year survival of 8% (95% CI 4–15%) in patients with local failure.

Local failures and local recurrences during follow-up were most probably treated with palliative TURB. Only 5 patients (3%) with recurrent cancer had a salvage cystectomy, while 17 patients (10%) received cisplatin-based chemotherapy. The 3-year and 5-year overall survival rate for all patients was 31% (95% CI 26–37%) and 21% (95% CI 16–27%), respectively (see Table 1).

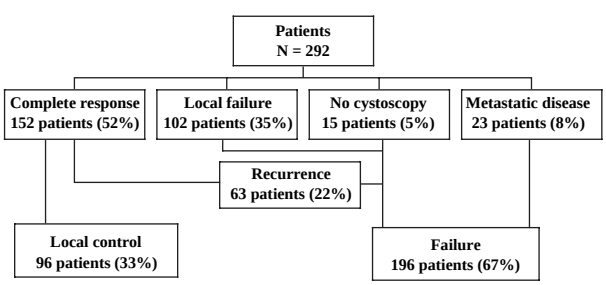

Fig. 1. Treatment outcome following radical radiotherapy. Fifteen patients (5%) died before the first 3-month cystoscopy. Twenty-three patients (8%) did not attend the 3-month control cystoscopy due to metastatic disease. Sixty-three patients (22%) had recurrent bladder cancer, 23 of those (8%) without evidence of local recurrent cancer.

Predictive factors for local control

Univariate analyses of patient-related factors revealed no association between gender or age and local control, while good performance status was significantly related to increased local control rate (see Table 1).

Among the tumor-related parameters, T-stage and the histology of the tumor were significantly related to local control. Lymph node stage had only borderline significance in relation to local control. No relationship between CIS, multiplicity of the tumor, or grade, and local control was found. Hydronephrosis, increased creatinine, and low hemoglobin, but not increased LDH, AP, and ALAT, were related to poor local control rate.

Complete macroscopic TURB was significantly related to improved local control, whereas treatment prolongation did not have any effect on local control.In the multivariate analysis, parameters with p-values of less than 10% in the univariate analysis were included except for N-status since the distribution of patients in each category prevented meaningful analysis. T-stage ($p < 0.01$), TURB ($p = 0.01$), and histology ($p = 0.02$) were independently related to local control (see Table 3).

Prognostic factors for overall survival

Tables 1 and 2 illustrate univariate analysis of possible prognostic factors in relation to overall survival. Performance status was the only patient-related factor significantly related to survival. At 3 years the oldest patients had the highest overall survival rate. This difference was, however, not statistically significant either when patients were categorized as younger or older than median age or in the five age groups in Table 1.

T-stage and N-stage were significantly related to overall survival. Other tumor-related parameters associated with overall survival were hydronephrosis, creatinine, hemoglobin, LDH, and AP but not ALAT.

Complete macroscopic TURB was significantly related to improved overall survival, whereas treatment prolongation did not have any effect on survival.

Prognostic factors with p-values of less than 10% in the univariate analysis were included in multivariate analysis except for N-status, LDH, and AP. N-status was not included, due to the distribution of patients in each group. LDH and AP did not meet the assumption of proportional hazards and, moreover, the use of a time-dependent model

Table 3

Summary of Cox proportional hazard analyses of significant covariates for local recurrences and overall survival

Factor	Category	Local control			Overall survival		
		Hazard rate (expβ)	95% CI.	p-value	Hazard rate (expβ)	95% CI.	p-value
Initial model							
T-stage	T1–T3a T3b–T4b	3.01	2.14–4.26	<0.01	2.33	1.76–3.06	<0.01
Haemoglobin	Normal Low	1.39	1.00–1.94	0.05	1.67	1.27–2.18	
Creatinine	Normal High	1.55	1.05–2.31	0.03	1.89	1.39–2.57	<0.01
Hydronephrosis	No Yes	1.61	1.15–2.25	0.01	1.91	1.45–2.50	<0.01
TURB	Complete Incomplete	2.92	1.91–4.46	<0.01	2.04	1.51–2.74	<0.01
PS	0–1 ≥2	2.17	1.17–4.03	0.03	3.79	2.51–5.73	<0.01
Histology	Transitional Mixtures	1.13	1.01–1.25	0.03	1.09	0.99–1.19	0.08
Final model							
T-stage	T1–T3a T3b–T4b	2.22	1.42–3.12	<0.01	1.48	1.09–2.02	0.02
PS	0–1 ≥2	–	–	NS	3.61	2.32–5.64	<0.01
TURB	Complete Incomplete	2.04	1.26–3.28	0.01	1.89	1.30–2.75	<0.01
Hydronephrosis	No Yes	–	–	NS	1.51	1.13–2.01	0.01
Creatinine	Normal High	–	–	NS	1.38	1.00–1.90	0.03
Histology	Transitional Mixtures	1.14	1.02–1.27	0.02	–	–	NS

NS: not significant.

would be difficult owing to the limited number of abnormal values. Performance status ($p < 0.01$), TURB ($p < 0.01$), hydronephrosis ($p = 0.01$), T-stage ($p = 0.02$), and creatinine ($p = 0.03$) were independently related to overall survival (Table 3, Figs. 2–4).

Complications

During radiotherapy, 78% of the patients experienced acute transient side effects such as diarrhea and cystitis requiring medication. Nine patients (3%) experienced severe bowel complications, resulting in treatment related deaths due to ileus in 5 patients (2%). Another 4 patients (1%) had their treatment cancelled due to ileus in 3 patients, and due to a rectal abscess requiring surgery in a fourth patient. Mean number of fractions from start of radiotherapy to severe bowel complications was 20 fractions (range 10–30 fractions). Six patients (2%) had a myocardial infarction, resulting in the death of 4 patients (1%), while the remaining two patients survived. The mean number of fractions from start of radiotherapy to myocardial infarction was 4 fractions (range 2–29 fractions).

Late complications (> 3 months following radiotherapy) requiring surgery were recorded in 13 patients (5%). Ten patients (3%) experienced radiation-induced ileus requiring surgery, which resulted in the deaths of two patients (0.7%), while the remaining eight patients (3%) survived following surgery. Three patients (1%) experienced severe radiation reactions in the bladder requiring surgery as a result of bladder fistulas in two patients, and a contracted bladder in a third patient. The median time from radiotherapy to the late radiation effects was 13.5 months (3–54 months). The actuarial risk of developing intestinal or bladder complications requiring surgery was 15% (95% CI 8–28%) during the 5-year period from the start of radiotherapy.

DISCUSSION

In this study, a complete response 3–4 months following radiotherapy was reported in 152 patients (52%) (see Fig. 1). Other studies have found complete response ranging from 44% to 80%. However, direct comparison of results between retrospective series is often difficult due to unknown or unrecorded biases. Moreover, complete response is assessed differently in different studies and does not always include a histological confirmation (5, 9, 11, 14, 17, 24, 25). Even though a complete response was an independent factor for survival ($p < 0.01$) in accordance with other studies (5, 9, 11, 14, 17, 25) it should be interpreted with caution. Patients achieving a complete response may represent a selected group with a better prognosis from the very beginning. On the other hand, if a complete remission was not associated with prolonged survival, one could doubt that radiotherapy had an impact at all.

The 3-year and 5-year overall survival rate of 31% and 21%, respectively, is consistent with previous studies in which patients for radiotherapy have been negatively selected (12–18, 24). Compared with series of patients undergoing radical cystectomy for bladder cancer, these survival rates are inferior (26, 27). This difference is attributed to the negative selection of patients for radiotherapy (28). Furthermore, understaging in TURB specimens compared with cystectomy specimens can induce a stage-migration effect in the group of patients undergoing cystectomy (29).

To improve the response rate and survival following radiotherapy, new treatment techniques with a higher conformity index such as intensity-modulated radiotherapy

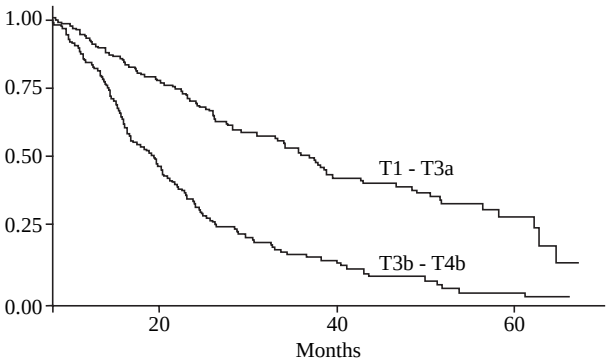

Fig. 3. Survival according to clinical T-stage.

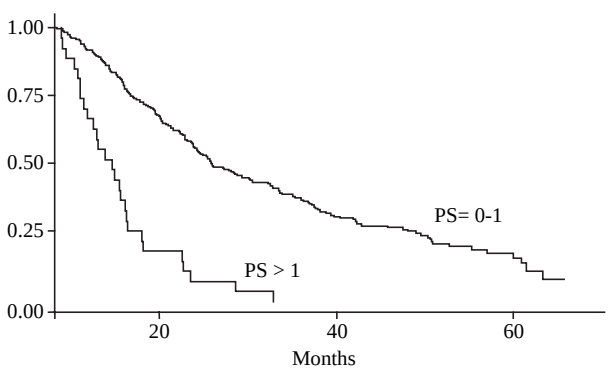

Fig. 2. Survival according to performance status (PS).

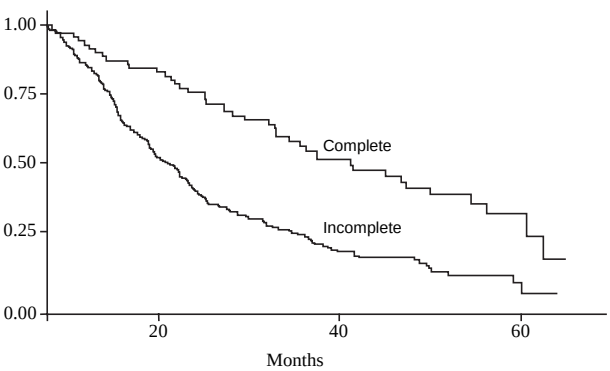

Fig. 4. Survival according to TURB.

should be investigated in randomized trials as a tool to facilitate safe dose escalation (24, 30). Furthermore, in selected patients, the use of chemotherapy administered concomitantly with radiotherapy may be a promising strategy (31).

In our study, 23 patients (8%) died of distant metastases diagnosed less than 3 months following radiotherapy. Another 23 patients (8%) subsequently died from distant metastasis without evidence of local recurrence (see Fig. 1). This illustrates the need for an effective systemic adjuvant treatment for patients who have an increased risk for subclinical distant metastases at the time of the initial diagnosis (28).

At cystoscopy 3–4 months after radiotherapy, local failure was observed in 102 patients (35%). Moreover, 40 of the patients (26%) with an initial complete response developed local recurrent cancer later on. Only 5 patients (3%) with local failure or local recurrence had a salvage cystectomy. In other studies, the frequency of salvage cystectomy following radiotherapy ranges from 11% to 20% (4–8, 25), which is a considerably larger number as compared with the present study. However, it should be emphasized that the low number of salvage cystectomies in our study is attributed to the fact that patients were selected for radiotherapy because of contraindications to surgery.

Some previous studies have found that elderly patients have a shorter survival than younger patients (7, 10, 12, 17). We found no statistical significance between age and local control or survival. Thus, age by itself should not be considered a poor prognostic factor, in agreement with a previous study showing that elderly patients with good prognostic factors may benefit from radical radiotherapy (32).

No association between gender and survival was found in the present study. This is in accordance with previous studies (2), with except from one study reporting a poorer survival among females following radiotherapy (4).

Performance status is usually of important prognostic value (2, 4, 18). Accordingly, we found performance status to be the most important prognostic variable independently related to survival (Table 1, Fig. 2). Even though the performance status was scored retrospectively from medical records, other studies have shown that the assessment of performance status when categorized in two groups is a valid method with prognostic information (21, 32). The present study confirms this fact, and demonstrates that the general condition of the patient should be evaluated when patients are selected for radical radiotherapy. The most consistent prognostic variable reported in the literature is the T-stage (2). Thus, we also found T-stage to be independently related to local failure and overall survival (see Table 3, Fig. 3).

Analyses of N-stage revealed a better survival in patients without lymph node metastases as compared with patients with known lymph node metastases or without lymph node staging. Patients with N1-disease had more local failures as compared with patients without lymph node staging. However, the 3-year and 5-year survival rates were comparable in the two groups (see Table 2). An explanation for this observation may be attributed to selection bias. As lymph node staging only was routinely performed in patients with good performance status, initially scheduled for cystectomy, and then referred for radiotherapy in the case of node-positive disease, patients with good performance status are selected to the N-positive groups. Patients with N2 disease had a poor local control rate as well as survival. A treatment strategy for these patients should include primary chemotherapy followed by radical radiotherapy, in responding patients.

Histology, i.e. pure transitional carcinoma vs. mixed tumor and pure squamous cell carcinoma, was independently related to local control but not to overall survival (see Table 3). In a previous study, squamous cell histology was associated with an increased risk of salvage cystectomy (7). These results confirm that squamous cell tumors may have a lower radiosensitivity as compared with pure transitional cell tumors.

Patients with pure transitional tumors predominantly had a Bergkvist grade 3–4. In univariate analysis, a relation between increasing grade and shorter survival was observed. However, this relation did not reach statistical significance. Some previous studies have found low grade related to increased survival (5, 11, 33), while other studies, in accordance with the present study, have not found any prognostic information on the tumor grade (4, 12, 14, 16, 17, 24, 25, 32).

In three previous studies carcinoma in situ and multiplicity of the tumor have been related to local recurrence, but not to survival (12, 16, 25). This is in contrast with our findings and a fourth previous study (4), in which no relation between local control and carcinoma in situ or multiplicity was found.

Previous reports on prognostic variables in bladder cancer have found impaired renal function, i.e. hydronephrosis and increased creatinine significantly related to poor survival (4, 9, 15, 17, 25). In our study, hydronephrosis as well as creatinine was independently related to overall survival but not to local control.

Other pre-treatment blood tests revealed a relation between low hemoglobin and local failure as well as poor overall survival in univariate analyses. This relation could not be established in the multivariate analysis (see Table 3), This result is in agreement with one previous study (14), but is contrary to two other studies on radiotherapy for bladder cancer in which an independent relation between anemia, local failure, and survival has been found (16, 33).

Increased AP and LDH were prognostic variables for overall survival but not for local control in the univariate

analyses. Follow-up revealed metastases in significantly more patients with high AP ($\chi^2 = 4.41$, $p = 0.041$) as compared with patients with a normal value. A relation between high LDH and metastatic disease could not be established ($\chi^2 = 1.12$, $p = 0.217$). This result suggests that high AP may be a predictor for metastasis in patients referred for radical radiotherapy, as well as an important prognostic variable for survival.

In the present study, only 21% of the patients had a macroscopic complete TURB prior to radiotherapy. This prognostic factor was independently related to local control and overall survival. Two previous studies have found macroscopic complete TURB independently related to overall survival (14, 15), while a third study found the prognostic value of a macroscopic complete TURB inferior to T-stage (12).

During radiotherapy, most patients experienced irritant bladder symptoms and diarrhea, which were manageable by medication. Nine patients developed severe bowel toxicity requiring surgery during radiotherapy.

Another 10 patients developed late radiation-induced ileus during follow-up. Severe bladder toxicity was reported in three patients during follow-up. The actuarial 5-year risk for side effects requiring any kind of surgery was 15% (95% CI 8–28%). In other studies, actuarial 5-year bowel and bladder side effects are reported in 4.1–12% and 1.2–11.5% of the patients, respectively (4, 5, 13, 25).

Nine patients died during treatment. In 5 of those, the cause of death was treatment related, while the remaining 4 patients died of causes not directly related to radiotherapy. During follow-up 2 treatment-related deaths due to late radiation-induced ileus were recorded. In total, 7 patients (2%) died as a result of complications attributable to radiotherapy. In other studies treatment-related deaths are reported in a similar range of 1.2% to 3.9% (4, 5, 18).

Owing to the retrospective design of the studies, the interpretation of the results on late effects is difficult. In our experience, late toxicity, especially the milder degrees not requiring medication or surgery, is often underestimated due to lack of registration. In general, this is important to note when interpretations of retrospective date on morbidity are performed. To give a more accurate description of side effects following radiotherapy we have reported only grade 3 and 4 toxicity, i.e. side effects that required surgery. To establish knowledge concerning milder degrees of late toxicity, all patients alive in the present study have been invited to participate in a structured telephone interview concerning late effects following radiotherapy. These data are published in a separate paper (34).

CONCLUSION

Performance status, T-stage, macroscopic complete TURB, hydronephrosis, and serum creatinine were independent prognostic factors for overall survival, and, thus, important for the selection of patients for curative intended radiotherapy. Patients with N1 disease had a reasonable prognosis following radical radiotherapy, while patients with N2 disease were less likely to benefit from radical radiotherapy. These patients should be offered primary cisplatin-based chemotherapy, followed by radical radiotherapy in the case of a response.

Radiotherapy was associated with acute transient side effects in 78% of the patients. Moreover, 7 treatment-related deaths (2%) were recorded, i.e. 5 patients died during radiotherapy, and another 2 patients died following surgery for late radiation-induced ileus. During the 5-year period from start of radiotherapy, the actuarial risk of complications requiring surgery was 15%.

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