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EXTERNAL BEAM RADIATION TREATMENT OF URINARY BLADDER CARCINOMA

An analysis of results in 203 patients

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Abstract

In a retrospective study, 203 patients with cancer of the urinary bladder were analysed concerning treatment outcome, survival and some prognostic factors. Radiotherapy with curative intent and a tumour dose of 66 Gy in 9 weeks with a 3 weeks' pause after 33 Gy was the planned treatment for 155 patients. Preoperative radiotherapy with a tumour dose of 40 Gy in 4 weeks was delivered to 28 patients, 4–6 weeks prior to cystectomy. Twenty patients with advanced disease received palliative radiotherapy with a tumour dose of 30 Gy in 2 weeks. A significant initial response to radiotherapy was obtained in 26.7% of the patients. The actuarial 5-year survival was 24% for patients treated with definitive radiotherapy only. The most important factors associated with survival in this radiotherapy group were stage (T-class), performance status and serum creatinine. Acute side-effects were common and in 18% of the patients deviation from the planned treatment was necessary.

Key words: Urinary bladder cancer, external radiotherapy, local control, survival, prognostic factors.

The incidence of transitional cell carcinoma of the urinary bladder is increasing in Finland (1). At the time of diagnosis 20–25% of the patients have lesions infiltrating the muscle wall (UICC T-stages 2–4) and approximately 5% have clinically metastatic disease (2, 3). The overall 5-year survival rate for invasive tumours is less than 50% and remains around 50% even if the primary tumour has been controlled (3). High grade or deeply infiltrating bladder cancer is usually treated with preoperative radiotherapy and cystectomy with the aim of curing the disease. Patients unsuitable for cystectomy often have advanced disease or poor general condition. They are treated with external radiotherapy. However, there is still controversy concerning the optimal dose, fractionation schedule as well as indications for preoperative or definitive radiotherapy. The aim of this retrospective study was to evaluate the outcome in urinary bladder carcinoma patients treated with definitive, preoperative or palliative radiotherapy.

Material and Methods

Between 1978 and 1984, 203 patients with carcinoma of the bladder were treated with external radiotherapy. This period was chosen for analysis due to the homogeneity in treatment techniques and dosages. One hundred and fifty-five patients received full dose split-course radiotherapy (4) with curative intent. A small group (28 patients) was treated with preoperative radiotherapy and cystectomy. Another minority (20 patients) received palliative radiotherapy only.

All tumours were classified according to the UICC TNM-system and the WHO malignancy grading system (5). The pathological reports and corresponding histological slides were reviewed by an experienced pathologist as to histological grade and the presence or absence of muscle invasion. The urological procedure prior to radiotherapy was cystoscopy and biopsy in 89 (43.8%), transurethral resection (TUR) in 66 (32.5%), partial cystectomy in 43 (21.2%) and cystectomy in 5 (2.5%) patients. After cystectomy 3 patients received postoperative radiotherapy with 'curative' dose and 2 patients radiotherapy with purely palliative intent.

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The performance status was estimated using the Karnofsky scale (6) and the degrees of acute and late side-effects were recorded during examinations of the patients.

Patients were treated with 6 or 8 MV photons from linear accelerators or with 33 MV photons from a betatron, each field being exposed daily. For some patients receiving palliative treatment, cobolt-60 or orthovoltage roentgen therapy was applied. The opposed pelvic fields (15 × 15 cm) were used for preoperative, palliative and the first part of definitive radiotherapy. The daily midplane dose was 2 Gy in the preoperative and 2–2.2 Gy in the split-course regimen. The target absorbed dose was 40 Gy delivered in 20 or 18 fractions over 4 weeks for the preoperative and the first part of the definitive treatment. A 3-week rest interval was taken after the first 3 weeks of the definitive treatment and the second part of the course was given with a 3-field technique (two oblique anterior and one posterior field) with field sizes usually varying from 8 × 10 to 10 × 10 cm. The planned total dose in the bladder was 66 Gy over 9 weeks. Ten fractions with 3 Gy was usually given for palliative treatment. Total cystectomy was performed about 4 weeks after the preoperative treatment.

Patients were followed by a urologist after cystectomy and by an oncologist after radiotherapy. Control cystoscopies were carried out at the referring urological departments 3 months after radiotherapy and then regularly at 3 to 6-month intervals. A reduced stage observed at control cystoscopy or in a cystectomy specimen as compared to the original clinical assessment is referred to as 'stage-reduction'. Local failure was defined as the presence of tumour in the bladder and/or pelvis within the treated volume after radiotherapy. Local recurrences were usually treated with transurethral resection sometimes combined with intravesical cytotoxic agents. Nodal metastases outside the treatment volume or hematogenous spread were defined as distant metastases. Systemic therapy was not usually considered for these patients. The follow-up time for 68% of the patients was longer than 5 years and the median follow-up time was 73 months.

Statistical parameters were evaluated using the BMDP-87 computer program (7). For comparison of frequencies the uncorrected χ^2-test was applied. The survival curves were constructed by the life-table method (BMDP program 1L) from the start of radiotherapy. BMDP program 1L was used to compare the survival of subgroups defined by possible explanatory variables using the log-rank test. The results of these analyses indicated which variables might reasonably be considered in the multivariate analysis. Program 2L of the BMDP-87 series (regression with incomplete survival data) was used in a forward stepwise mode to assess the simultaneous effects of multiple prognostic factors. Separate regression analyses were performed (and compared) for the total material and for different treatment groups. P-values <0.05 were considered statistically significant.

Results

The distribution of patients by age, Karnofsky index, and treatment group is presented in Table 1. The difference between the number of patients with poor (<70) performance status in the different treatment groups was highly significant ($p < 0.0001$). There was an association between a poor Karnofsky index and the presence of metastatic disease ($p < 0.05$).

The male/female ratio was 3 : 1. Hematuria was the first symptom in 163 patients, dysuria with or without hematuria in 38 and in 2 patients the diagnosis was incidental.

Concerning histological subtypes 188 patients (92.6%) had transitional cell carcinoma, 4 (1.9%) squamous cell carcinoma, and 11 (5.4%) anaplastic cancer. The distribution of the patients according to T-category and treatment group is presented in Table 2.

Based on clinical examination and/or computed tomography node involvement was suspected in 28 (13.8%) patients prior to radiotherapy. Classification of the transitional cell carcinomas revealed that 107 (56.9%) were grade 3, 76 (40.4%) grade 2, and 4 (2.1%) grade 1.

Diagnostic stage and grade in the definitive radiotherapy group. The survival rates in various T-categories differed significantly from each other ($p < 0.001$, Fig. 1) with lower rates in the more advanced stages. The differences according to surgical treatment before radiotherapy between T-categories were not significant. The differences in distribution of patients in T-categories according to local tumour status after radiotherapy are shown in Table 3. The difference in response to definitive radiotherapy in different tumour categories was not significant ($p > 0.05$).

Table 1

Distribution of patients by age, performance status (Karnofsky index) and treatment group

Radiotherapy	Number of patients	Karnofsky under 70	Age mean	(years) range
Definitive	155	30 (19%)	68.2	28–88
Preoperative	28	1 (4%)	62	40–77
Palliative	20	14 (74%)	72.5	51–86
Total	203	45 (22%)	67.6	28–88

Table 2

Distribution of patients according to T-category in different treatment groups

Radiotherapy	n	Percentage				
		T1	T2	T3	T4	TX
Preoperative	28	–	28.3	13.3	2.9	
Definitive	155	93.3	65.2	75.3	88.3	
Palliative	20	6.7	6.5	11.4	8.8	100

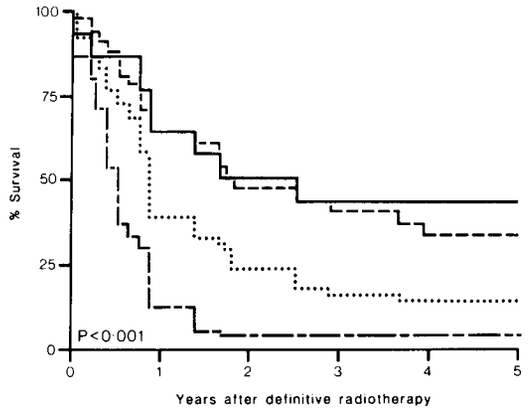

Fig. 1. Actuarial survival for patients by tumour category: T1 (——, n = 14), T2 (— —, n = 30), T3 (· · ·, n = 79), T4 (- — -, n = 30), ($p < 0.001$).

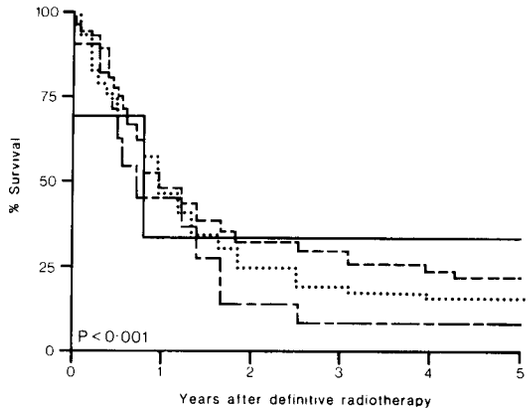

Fig. 2. Actuarial survival by histological grade: grade 1 (——, n = 3), grade 2 (— —, n = 56), grade 3 (· · ·, n = 84), not estimated (- — -, n = 12).

Survival curves according to grade are presented in Fig. 2. There were only 3 patients with a grade 1 tumour. The differences between survival rates in the various grades were statistically significant (over $p < 0.001$).

Treatment response and disease specific survival. The tumour status in the bladder after radiotherapy could be evaluated in 128 patients treated with definitive radiotherapy. Stage reduction and local control were observed in 34 of the patients (26.6%). In 94 (73.4%) tumour status in the bladder after radiotherapy did not significantly differ from the original clinical assessment. A tumour-free bladder or stage reduction after partial resection or radiotherapy was observed in 48% of patients, compared to 28% after transurethral resection and 13% after biopsy and radiotherapy. The difference in the proportion of patients with stage reduction according to different preradiotherapy treatment was significant (overall $p < 0.01$, Table 4) indicating higher probability of local control when more extensive surgery preceded definitive radiotherapy.

After preoperative radiotherapy 29.6%, and after preoperative radiotherapy and cystectomy 44%, of the patients experienced local control. The corresponding proportion for patients after definitive radiotherapy was 26.6%. The difference was not statistically significant ($p > 0.05$). The 5-year survival rate for all patients showing initial stage-reduction (77%) was significantly better ($p < 0.001$) than the rate for those without such improvement (18%).

Multifactorial analysis. Primary stage, Karnofsky index and creatinine level were the three most important prognostic variables associated with survival in all patients after radiotherapy. Table 5 presents the regression coefficients and standard errors for the most important variables in the entire series and in the group of patients treated with definitive radiotherapy. In a separate analysis of the patients receiving definitive radiotherapy performance status, T-class and creatinine level remained significant prognostic factors.

The 5-year survival of patients in the definitive radiotherapy group with lymph node metastases at the time of diagnosis was 16% compared to 20% for patients without evident lymph node metastases ($p < 0.05$, Fig. 3). All patients with distant metastases died within a year after radiotherapy. The incidence of positive nodes in patients who had a good response to irradiation was 2/34 (5.9%). Positive nodes were found in 18/94 (19%) patients showing no stage-reduction. Patients who survived were on average younger (mean 64.8 years) than patients with a poor outcome (mean 68.6).

The disease specific actuarial survival curves for different treatment groups are presented in Fig. 4. The survival rates in the treatment groups differed significantly from each other ($p < 0.001$). The combination of preoperative radiotherapy and radical cystectomy resulted in a 5-year survival of 50%, compared to 24% for definitive

Table 3

Distribution of patients according to T-category and response (local control or stage reduction after definitive radiotherapy) (overall $p > 0.05$)

	Percentage				
	T1	T2	T3	T4	Total
Local control/stage reduction	15	35	28	14	26
No response	85	65	72	86	74

Table 4

Tumour status after definitive radiotherapy related to preradiotherapy surgical treatment (overall $p < 0.01$)

	Local control	Not improved
Biopsy	6/47 (13%)	41/47 (87%)
TUR	13/47 (28%)	34/47 (72%)
Partial resection	15/31 (48%)	16/31 (52%)

Table 5

Values of statistically significant regression coefficients from the stepwise Cox's regression analysis (Karnofsky and creatinine used as continuous variables)

Variable	Coefficient		Standard error	
	all patients	definitive group	all patients	definitive group
Primary T-category	0.2121	0.2601	0.0549	0.0612
Karnofsky	−0.0219	−0.0187	0.0081	0.0091
Creatinine	0.0027	0.0027	0.0012	0.0012

radiotherapy. After palliative radiotherapy only two of the patients survived over a year and one over 5 years.

Side-effects and complications. In 27 patients the treatment was interrupted due to dissemination of the disease, deterioration of the condition of the patient or severe gastrointestinal side-effects. In the definitive radiotherapy group 12%, in the preoperative group 3.5%, and in the palliative group 39% of the patients interrupted the treatment. Grade 1 to 3 gastrointestinal acute side-effects were observed in 52% and symptoms of cystitis during radiotherapy in 57% of the patients. Signs of radiation cystitis at cystoscopy were observed in 17% of the paatients. Seven patients (3.5%) died of complications during the observation period. Four of them died within 3 months after preoperative treatment (40 Gy in 20 fractions) due to small intestinal occlusion and ileus (3 patients) or fibrinous peritonitis (one patient). Two patients in definitive radiotherapy group had received 66 Gy (with 2.2 Gy fractions) and died about two years after the treatment due to intestinal occlusion and ileus; both of them also had tumour recurrences. One patient died two months after definitive radiotherapy due to septic urinary infection which had started already during the treatment.

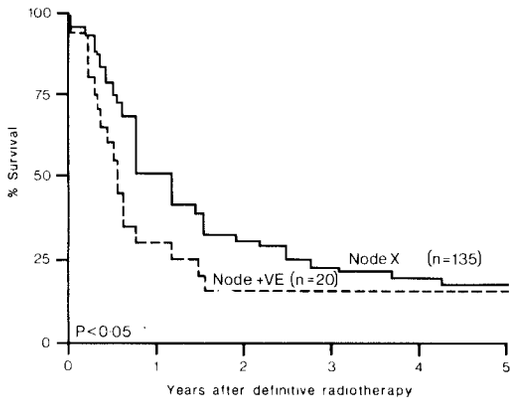

Fig. 3. Actuarial survival after external radiotherapy related to nodal status prior to radiotherapy: lymph node metastases (——, n = 20), no metastases defined (——, n = 135).

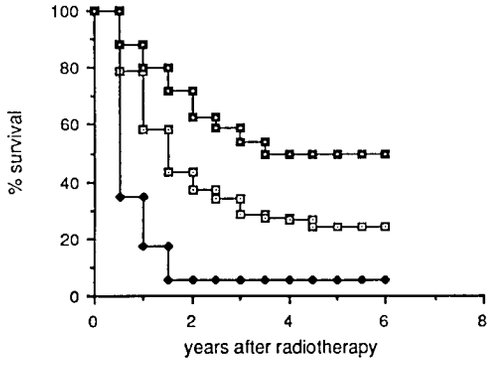

Fig. 4. Actuarial survival for different treatment groups: preoperative and cystectomy (□, n = 28), definitive radiotherapy (⊡, n = 155), palliative radiotherapy (◆, n = 20). ($p < 0.001$).

Discussion

External radiotherapy for cancer of the urinary bladder is usually a secondary choice of treatment although some tumours with muscle infiltrations can be eradicated by radiation therapy alone (8). Patients with a prior history of bladder cancer have a poorer outcome than patients accepted for primary treatment (9). The preradiotherapy performance status, tumour status in the bladder and pretreatment creatinine were in the present study independent factors associated with survival in the present study. The prognostic importance of ureteric obstruction, often indicating poorer prognosis has been previously suggested by Edsmyr et al. (10) and Shipley et al. (11). According to Spera et al. (12) patients with abnormal creatinine levels had a decreased survival that was independent of stage. In a recent multifactorial analysis by Mameghan & Fisher (13) of 205 invasive urinary bladder cancer patients clinical stage and ureteric obstruction were significant prognostic factors. The prognostic importance of the Karnofsky index in T4 bladder cancer patients has been reported by Fosså et al. (14). Hanks (15) stated that prostate carcinoma patients with a poor Karnofsky function have an increased chance of dying, due to both intercurrent health factors and cancer. This is probably true also for urinary bladder cancer patients.

If the patients had been matched according to stage, age and general condition, the results for preoperative radiotherapy and surgery or definitive radiotherapy might have

been more similar (13, 16). As pointed out by Radwin (17) and Droller (18) case selection within apparently comparable tumour categories may largely influence the end results. In the present study it was obvious that different pretreatment characteristics and selection factors influenced the results in the different treatment groups.

Both type of radiation treatment and extent of transurethral surgery may influence the risk of local recurrence after treatment (11). Stage reduction has been shown to predict fewer recurrences and improved survival (16, 19–21). Also in our patients stage reduction indicated survival advantage.

Tumour grade showed in the present study a statistical correlation to survival in the definitive radiotherapy group when examined singly but not in the multivariate analysis. This finding is in agreement with a report by Duncan & Quilty (22). Based on evidence from earlier studies Whitmore (3) stated that characterization of tumours in terms of grade and T-category alone provides an insufficient basis for selection of treatment and for analysis and interpretation of end results. Tumour heterogeneity within a specific grade and T-category and the general condition of the patient have an important influence on the end results.

The results of the multivariate analysis for the heterogeneous group of patients in the present study indicate that the apparent effects of treatment are to a large extent due to patient selection.

Radiotherapy of invasive bladder cancer can improve both pelvic control and survival (11). The radiation doses used for transitional cell urinary bladder cancer range from 50 to 70 Gy in 5 to 8 weeks (23) and various radiation techniques have been employed. According to Morrison (24) the tumour control rate is highly dose-dependent for patients with transitional cell carcinoma. He showed that with increasing tumour dose from 42.5–63.5 Gy the control rate increased from 38 to 80%. For definitive treatment the general policy is to administer the maximum tolerable dose in the bladder. In the present material the total planned dose was 66 Gy. However, local control rate and survival after definitive split-course radiotherapy were relatively low compared to some reported results (25, 26). Our actuarial 5-year survival of 24% was, however, similar to that reported by Mameghan & Fisher (13) after definite continuous radiotherapy.

More than 40% of our cystectomized patients developed metastases after treatment and died of bladder cancer. This indicates underestimation of the pretreatment nodal status. Improvement in staging and diagnostics could save some of these patients from unnecessary major therapeutic procedures.

A split-course interval during irradiation improves the patient's tolerance, but has been criticized for allowing repopulation of even causing accelerated repopulation of the tumour cells (27, 28). However, no significant differences have been observed between results after split-course or continuous treatment of urinary bladder cancer when the total dose in split-course treatment has been increased to compensate for the break in the treatment (29). The tolerance can also be improved by using a 4-field technique or by reducing the fraction size as reported by Edsmyr et al. (30) and Cox et al. (27).

Radiotherapy of bladder cancer may cause severe acute side-effects and even life-threatening intestinal complications in some of the patients. The treatment mortality rate of 3.9% seen in the present series is in agreement with some earlier reports (22, 31). However, the real proportion of late side-effects is difficult to estimate. Several studies (22, 32–35) indicate that the late side-effects of radiotherapy can be significantly reduced by optimum treatment planning, which has to be tailored according to the extent of the tumour and regional spread.

The results in patients with more advanced disease and the relatively high number of patients who interrupted even palliative treatment support the suggestion by Quilty et al. (36), Fosså et al. (14) and Shehata et al. (33) that patients with advanced pelvic disease or distant metastases should be spared high-dose pelvic irradiation. These patients often benefit more from simple surgical procedures or short-course palliative radiotherapy.

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