A Randomized Trial of Radical Radiotherapy for the Management of pT1G3 NXM0 Transitional Cell Carcinoma of the Bladder

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Purpose: We conducted a multicenter randomized trial in the United Kingdom to determine the efficacy of radical radiotherapy in reducing the incidence of progression of pT1G3 transitional cell carcinoma of the bladder to muscle invasive disease and subsequent disease fatality.

Materials and Methods: Patients with a new diagnosis of pT1G3 NXM0 transitional cell carcinoma with unifocal disease and no carcinoma in situ (group 1), or with multifocal disease and/or carcinoma in situ (group 2) were eligible for the trial. Patients in group 1 were randomized between observation and radiotherapy to the bladder, and in group 2 between intravesical therapy and radiotherapy.

Results: From September 1991 to February 2003 a total of 210 patients from 37 centers in the United Kingdom were entered into the study. There were 77 patients in group 1 and 133 patients in group 2, and 6 patients were excluded from analysis because they were found to have pT2 disease by the reference pathologist. No evidence of an advantage with radiotherapy was found in terms of progression-free interval (hazard ratio 1.07; 95% CI 0.65, 1.74; p = 0.785), progression-free survival (hazard ratio 1.35; 95% CI 0.92, 1.98; p = 0.133) or overall survival (hazard ratio 1.32; 95% CI 0.86, 2.04; p = 0.193).

Conclusions: To our knowledge this is the largest randomized trial performed in patients with pT1G3 disease for which 210 patients were recruited during 11 years. There is no evidence that radiotherapy is better than more conservative treatment. The prognosis of this group of patients appears to be poor irrespective of treatment and new treatment strategies need to be investigated.

Key Words: urinary bladder neoplasms, randomized controlled trials, radiotherapy

Bladder cancer is the fifth most common cancer in the United Kingdom with 10,000 new cases recorded in 2003 and 356,000 cases worldwide.[1] Whereas bladder cancer invasive of the basement membrane as far as the lamina propria (pT1) can be treated successfully with endoscopic resection alone, a proportion of cases has progression to a more invasive and usually incurable disease stage. This is particularly true of cases with high grade histology, pT1G3 tumors, which have a long-term progression rate in the region of 40%.[2] Approximately 9% of superficial TCC of the bladder cases are T1G3 in British practice.[3] While early cystectomy in superficial TCC has a low mortality from bladder cancer, this has to be weighed against the effect of radical cystectomy on patient QOL. Adjuvant therapy with intravesical chemotherapy and BCG is frequently given although the long-term benefit appears to be modest, with evidence of an effect on recurrence but with a more limited effect on progression.[4,5]

Adjuvant radiotherapy has been given for T1G3 bladder cancer at certain centers in the United Kingdom. Their reports of patients treated with radiotherapy are encouraging.[6,7] One center in particular found that 40% of patients had recurrence following radiotherapy and no patient who remained disease-free for 6 months had a subsequent recurrence with a 5 to 10-year followup.[7] This impressive result in superficial disease accords with the greater sensitivity of grade 3 TCC of all stages to radiotherapy compared to the response of grades 1 and 2 tumors.[7] These studies had recurrence as the primary end point and it is not possible to assess whether tumor progression was prevented. Furthermore, radiotherapy to the bladder is not without cost to the patient because bladder and bowel toxicity is seen. A randomized study of early radiotherapy following the diagnosis of pT1G3 transitional cell carcinoma of the bladder was set up to address the question of whether any benefits in terms of progression and survival justify the toxicity.

MATERIALS AND METHODS

Patients

Eligible patients had a diagnosis of pT1G3 NXM0 tumor or tumors of the bladder, the diagnosis of this stage or grade

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Study received local ethics committee approval from all participating institutions.

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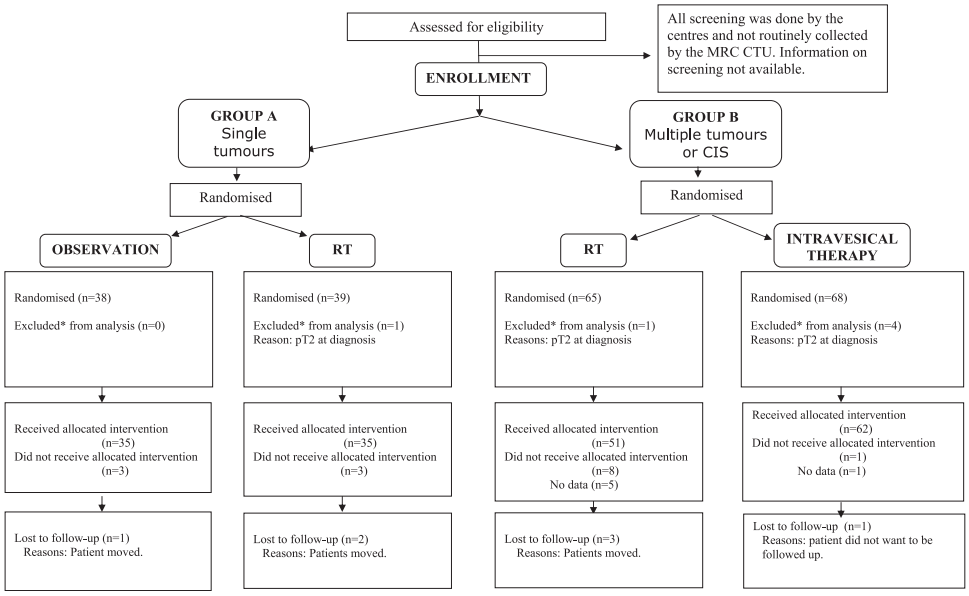

FIG. 1. Trial flowchart. Asterisk indicates that all patients excluded from analysis were assessed for inclusion/exclusion independently by reference pathologist blind to treatment assignment.

having been made for the first time within the previous 6 months, and muscle from the base of tumor which was histologically clear. A prior history of lower grade or stage bladder cancer was admissible but higher stage was not. Patients with widespread CIS causing severe symptoms were excluded but partial involvement of bladder or asymptomatic widespread CIS were both admissible. No prior therapy with intravesical chemotherapy or BCG (other than a single adjuvant treatment) was permitted. All visible tumors had to have been completely resected transurethrally. Only patients able to undergo radiotherapy and cystoscopic followup with biopsy were included. The study was approved by the local ethics committees of the participating institutions and all patients gave informed consent.

Study Design and Treatment

Figure 1 shows the trial schema. Collaborating surgeons were permitted to perform repeat cystoscopy and biopsy to confirm tumor stage and presence or absence of CIS. At this point the patients were placed in group 1—single tumors and no CIS or in group 2—multiple tumors or CIS. Patients in group 1 were randomized between observation and radiotherapy and in group 2 between radiotherapy and intravesical therapy. The treatment arms were observation, radiotherapy or intravesical therapy. For observation no treatment other than TUR was given before cystoscopy at 3 months. After this time treatments could be given as clinically indicated. For radiotherapy the patient could be treated using a 3 or 4-field technique with megavoltage irradiation to the bladder only, all fields being treated at each visit avoiding a variation of dose wider than ± 5% across the target volume. The dose to the posterior rectal wall was not to exceed 75% of the prescribed dose. The prescribed dose was 60 Gy in 30 fractions during 6 weeks or its equivalent if a shorter fractionation schedule was preferred. If the computerized tomography planning scan

TABLE 1. *Patient characteristics*

	Group 1		Group 2		
	Observation	RT	RT	MMC or BCG	Totals
No. sex (%):					
Male	32 (84)	35 (92)	54 (84)	52 (81)	173 (85)
Female	6 (16)	3 (8)	10 (16)	12 (19)	31 (15)
Age:					
No. 60 or younger (%)	8 (21)	10 (26)	7 (11)	13 (20)	38 (19)
No. 61–70 (%)	12 (32)	14 (37)	26 (41)	24 (38)	76 (37)
No. 71–80 (%)	16 (42)	12 (32)	27 (42)	24 (38)	79 (39)
No. older than 80 (%)	2 (5)	2 (5)	4 (6)	3 (5)	11 (5)
Median (IQR)	70 (71, 76)	69 (59, 74)	70 (64, 75)	68 (63, 74)	69 (63, 74)
No. WHO performance status (%):					
0	28 (74)	30 (79)	48 (75)	47 (73)	153 (75)
1	10 (26)	7 (18)	15 (23)	15 (23)	47 (23)
2	0 (0)	1 (3)	1 (2)	2 (3)	4 (2)
No. max cm largest tumor diameter (%):					
2 or Less	20 (56)	19 (53)	42 (69)	44 (72)	125 (64)
2.1–5	16 (44)	14 (39)	18 (30)	15 (25)	63 (32)
Greater than 5	0 (0)	3 (8)	1 (2)	2 (3)	6 (3)
Missing	2	2	3	3	10
Totals	38	38	64	64	204