

Radical irradiation for carcinoma of the prostate

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Summary

Ninety-three patients treated by radical irradiation for stage A2, B and C1 carcinoma of the prostate between 1979 and 1988 at a joint radiotherapy service were reviewed. The average age was 63 years, 84% of the patients were white and on histological examination the tumours were well or moderately differentiated in 88% of cases. Treatment was with 5 fractions per week in 71% while the remainder received 3 - 4 fractions per week. At a median follow-up of 62 months, the 5-year survival rate was 83% and the relapse-free rate was 73% (life table). The most important prognostic factor was tumour grade. In patients with grade 1 and 2 tumours, the 5-year survival rate and relapse-free rate was 91% and 76% respectively, while the survival for grade 3 tumour was 60% and 22% respectively ($P < 0,05$ logrank). There was a suggestion that patients diagnosed by trans-rectal needle biopsy did better than those diagnosed by trans-urethral resection, but this was not statistically significant. Disease stage did not influence survival. The crude late complication rate was 10% but this was significantly related to the use of less than 5 fractions of radiation per week.

A separate group of 13 patients with local disease who had had failed previous hormonal treatment were not analysed. Their 5-year survival rate was 19%, which is statistically significantly worse ($P < 0,001$ logrank).

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Carcinoma of the prostate is the second most common carcinoma in Western countries.¹ Its incidence is low in Third-World populations living traditionally but increases with urbanisation and increased socio-economic status.¹ The definitive treatment of localised disease began in the first decade of this century when radical prostatectomy was performed by Young² in the USA. Long-term disease-free survival was obtained, but the side-effects were considerable — impotence in nearly all patients and urinary incontinence in many, so that the operation never became popular outside a few centres. Patients were generally either followed up only or, after the introduction of androgen ablation in the 1940s,³ treated palliatively by orchidectomy and/or oestrogens.

In the 1960s Bagshaw⁴ showed that treating localised prostatic carcinoma with external beam irradiation could result in high local control rates with relatively low morbidity. This was confirmed by other studies in the 1970s.⁵⁻⁷ Radical irradiation for carcinoma of the prostate began at the joint radiotherapy service of Groote Schuur Hospital, Cape Town; Provincial Hospital, Port Elizabeth; and Frere Hospital, East London, in 1979.

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A retrospective study was undertaken to evaluate the results of therapy, especially its toxicity, in view of the anticipated long survival of patients.

Patients and methods

Ninety-three patients, who were treated primarily with irradiation at our institutions in the 10-year period 1979 - 1988, were reviewed. An additional 13 patients, who had previously been treated by hormones for at least 2 months and who were subsequently irradiated, are also discussed (see 'Results').

All patients were staged⁸ (Table I) by clinical examination, 12-channel investigations, measurement of serum acid phosphatase levels, chest radiography and a bone scan. In more recent years, patients have also undergone pelvic computed tomography (CT) scans to evaluate pelvic adenopathy and serum prostatic antigen level determination.

TABLE I. STAGING SYSTEM FOR CARCINOMA OF THE PROSTATE

Stage	Indications
A1	Clinically occult, focus well differentiated
A2	Clinically occult, diffuse or poorly differentiated
B	Palpable tumour confined within prostatic capsule
C1	Palpable tumour extending beyond the prostatic capsule
C2	Massive extraprostatic tumour involving pelvic sidewall, bladder or rectal mucosa
D1	Regional lymph node metastases
D2	Skeletal/visceral metastases and distant lymph node metastases

The median age of patients was 63 years; age distribution is shown in Fig. 1. Further patient characteristics and the method of diagnosis is shown in Table II. The majority of patients (86%) were white, had well-differentiated tumours on histo-

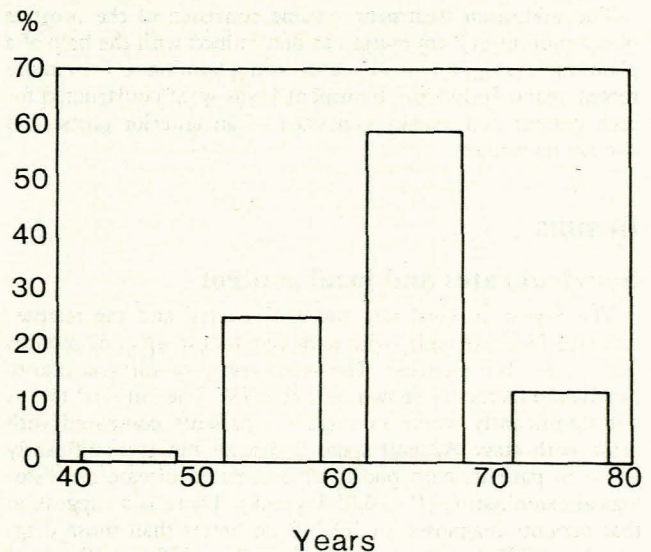


Fig. 1. Age distribution of patients.

TABLE II. PATIENT CHARACTERISTICS AND METHOD OF DIAGNOSIS IN 93 PATIENTS TREATED PRIMARILY WITH RADIATION

Race	
Whites	86%
Blacks	7%
Mixed	7%
Histology	
Grade 1	64%
Grade 2	24%
Grade 3	12%
Stage	
A2	9%
B	57%
C1	34%
Method of diagnosis	
TUR	68%
TRNB	27%
Prostatectomy	4%

logical examination (61%) and stage B disease (57%). The diagnosis was made by transurethral resection (TUR) in 68% and by trans-rectal needle biopsy (TRNB) in 27%. The prostatic acid phosphatase level was either normal or marginally elevated in all cases.

Most patients (71%) were treated with 5 fractions per week. The remainder were treated with either 3 or 4 fractions per week because of limited machine availability (Table III). Megavoltage radiation was used in all patients with either cobalt 60 or a 20 MV linear accelerator.

TABLE III. FRACTIONATION REGIMENS USED IN RADICAL IRRADIATION OF CARCINOMA OF THE PROSTATE

No. of patients	%	Fractionations/ wk	Dose/ fractionation (Gy)	Tumour dose (Gy)
66	71	5	2,0	60,0
16	17	4	2,4	57,6
11	12	3	3,0	54,0

The minimum treatment volume consisted of the prostate plus a minimum 2 cm margin as determined with the help of a planning cystogram in all cases and planning CT in more recent years. Individual treatment plans were constructed for each patient and usually consisted of an anterior portal and two lateral wedges.

Results

Survival rates and local control

The 5-year survival rate was 83% overall and the relapse-free rate 73% (life table) with a median follow-up of 62 months (range 12 - 106 months). The relationship of survival rate to prognostic factors is shown in Table IV. The survival rate is not significantly worse in stage C1 patients compared with those with stage A2 and stage B disease but is significantly worse in patients with poorly differentiated disease on histological examination ($P < 0,05$ logrank). There is a suggestion that patients diagnosed by TRNB do better than those diagnosed by TUR but this is not statistically significant. The local relapse-free rate is 93%.

TABLE IV. PATIENT SURVIVAL (LIFE TABLE) AND ITS RELATIONSHIP TO STAGE, HISTOLOGICAL GRADE AND METHOD OF DIAGNOSIS

	No. of patients	Overall survival (%)	Disease-free survival (%)
Total	93	83	73
Stage			
A2 and B	61	85	74
C1	32	83	70
Grade			
1 and 2	82	91	76
3	11	60	22
Diagnostic method			
TRNB	25	87	81
TUR	64	81	69

Relapse

Twelve patients have thus far relapsed, 6 with osseous metastases, 3 with metastases in the prostate gland and 3 with metastases in the draining lymph nodes. The median time to onset of relapse was 25 months overall, 18 months for osseous metastases and 36 months for nodal or prostate recurrence.

The relapse rate in patients with stage A2/B and stage C disease was 11% and 16% respectively. The relapse rate in patients with well-differentiated, moderately-differentiated and poorly-differentiated disease on histological examination was 7%, 14% and 45%, respectively. The latter is statistically significantly higher ($P < 0,001$, chi-square test). (These are crude figures and the relapse rate will increase with further follow-up.)

Complications

Complications were graded according to Radiation Therapy and Oncology Group (RTOG) system (Table V). The late complications and their relationship to the radiation fractionation used is shown in Table VI. The complication rate in patients treated with 3 - 4 fractions per week was statistically significantly higher than those treated with 5 fractions per week ($P < 0,001$, chi-square test). The complication rate of those treated with 3 fractions per week was also statistically significantly higher than those treated with 5 fractions per week ($P < 0,05$).

TABLE V. ABBREVIATED RTOG GRADING SYSTEM FOR COMPLICATIONS

Grade 2	Grade 3
Bladder	
Moderate frequency	Severe frequency
Generalised telangiectasia	Bladder capacity < 150 cc
Intermittent haematuria	Frequent haematuria
Small/large bowel	
Moderate diarrhoea	Obstruction or bleeding requiring surgery
Intermittent bleeding	

Patients who had undergone previous therapy

Thirteen patients were treated during 1979 - 1988 after having had hormonal treatment for more than 2 months before referral. They had all previously presented to local institutions with localised disease and either treatment had failed after

TABLE VI. LATE COMPLICATIONS AND THE CRUDE COMPLICATION RATE (%) AND THEIR RELATIONSHIP TO RADIATION FRACTIONATION SCHEDULE USED

Site	No. of patients	Complications		Complication rate
		Grade 2	Grade 3	
Bladder	93	3	1	4
Bowel	93	5	1	6
Fractionations/ wk				
3	11	2	2	36
4	16	2	0	13
5	66	4	0	6

hormonal therapy or they had responded poorly to therapy. The median age was 67 years (range 48 - 74 years). Stage B disease was present in 62% and stage C1 in 38%. On histological examination the disease was well or moderately differentiated in 77% and poorly differentiated in 23%. The survival rate was poor, being 59% at 3 years and 19% at 5 years. This was statistically significantly worse than the patients who had not had previous hormonal therapy (logrank) at both 3 years ($P < 0,05$) and also at 5 years ($P < 0,001$). Grade 2 complications occurred in 2 patients, giving a crude complication rate of 15%.

Conclusions

Carcinoma of the prostate may have a long natural history yet progressive disease is a major cause of morbidity and mortality in patients who do not have coexistent medical disorders. It is the third leading cause of cancer deaths in Western countries.¹ There are no published prospective randomised studies comparing radical irradiation to no treatment in patients with localised carcinoma of the prostate as these studies have failed to accrue sufficient numbers of patients. The critical review of results of therapy is therefore particularly important.

In an American pattern-of-care study⁹ of external beam irradiation for prostate cancer, the results of 682 patients treated in community hospitals were reviewed. These have been compared with the findings of the American College of Surgeons (ACS) in patients who were treated by hormonal therapy only or were followed up only.¹⁰ There was a clear benefit in survival at 5 years in patients treated with irradiation for stage A disease (85% v. 72%) and stage B disease (75% v. 68%). Survival was similar in patients with stage C disease (58% and 59%, respectively). It was, however, speculated that any benefit from hormonal therapy in stage C patients will be exhausted by 5 years and that there might be increased mortality in the group of patients who had not received radical therapy at between 5 years and 10 years. The 10-year survival rates in the American pattern-of-care study⁸ of irradiation for stage A, B and C disease were 61%, 46% and 38%, respectively, while there are no 10-year survival-rate figures available for the ACS series. In addition, patients with stage C disease were not divided into stage C1 and C2, which has been shown to be highly significant in patients treated with external beam irradiation.

In a recent study,⁸ patients with stage C1 disease had an overall survival and a relapse-free survival rate of 74% and

67%, respectively, while the corresponding figures in patients with C2 disease were 48% and 0%.

In our patients with stage A2 - C1 carcinoma, treated primarily with radiation, we observed a 5-year survival rate of 83% overall and 73% relapse-free rate at a median follow-up of 62 months. The local relapse-free rate was 93%. This is comparable to the findings in other studies.

The most important prognostic factor in our patients was tumour grade. In patients with grade 1 and 2 tumours, the overall 5-year survival and relapse-free rates were 91% and 76%, respectively, while the corresponding figures for patients with grade 3 disease were 60% and 22%, respectively. Disease stage in our series did not play a major role. Disease grade was also the most important prognostic factor in the RTOG analysis of 566 cases.¹⁰ Disease stage was not, however, an important prognostic factor in our patients, possibly because only patients with C1 disease were included. There was a suggestion that patients diagnosed by TRNB did better than those diagnosed by TUR. This has been discussed elsewhere.¹¹ The survival rate for patients in whom previous hormonal therapy had failed was statistically significantly worse. Hormonal therapy for asymptomatic patients with localised disease is not curative and cannot be recommended. In those patients who relapse after hormonal therapy, irradiation is unlikely to be curative and should be administered primarily with palliative intent.

The overall crude complication rate was 10%. This was strongly related to the radiation fractionation schedule and was statistically significantly higher in patients treated with fewer than 5 fractions per week.

We believe that these results support the continued administration of radical irradiation to selected patients with carcinoma of the prostate. This would include those who are free from coexistent medical disease that would impair their lifespan and with stage A2, B and C1 carcinoma. Poorly-differentiated disease on histological examination is a relative contraindication.

Deviance from conventional fractionation (5 per week) resulted in increased complications in this group of patients who have prolonged survival and is not recommended.

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