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# RADICAL RADIOTHERAPY IN PROSTATIC CARCINOMA

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**Abstract**

During the years 1978–1986 111 fairly elderly patients with prostatic carcinoma in clinical stages B, C, or D, and usually having tumours that were poorly differentiated, received radical radiotherapy to the prostate and bladder and to the adjacent lymph node regions. The side effects were comparable to those reported in the literature. During the follow-up 72% of the patients sooner or later (actuarial analysis) developed local recurrence or distant metastases. The projected survival rate at 8 years was 25%, and should be compared with the 65% expected for an age-matched Swedish male population. After 3 years the two survival curves became rather parallel, indicating a 'cure' rate of the order of 49%. There was a significant difference in survival between patients clinically judged to have only intracapsular carcinoma and those considered to have extracapsular carcinoma. The relatively modest survival figures in the present series reflect the malignant nature of poorly differentiated carcinoma of the prostate.

*Key words:* Prostatic cancer, radical radiotherapy, stage, grade, survival, side effects.

During the last few decades, there has been a rising interest in the radical treatment of localized prostatic carcinoma. Radical prostatectomy is now more often being considered in these patients. An alternative is radical radiotherapy, which has been used in some centres for very long. Thus, in particular, the Stanford experience (1) now includes almost 900 patients followed for up to more than 30 years.

In the radical radiotherapy of early prostatic carcinoma, the target volume(s), the target absorbed dose(s), and the treatment technique vary with time and between centres. Relatively large target volumes have often been used including the regional lymphatics in the pelvis and lumbar area. Other centres have, especially in recent years, used more limited target volumes, allowing a larger radiation dose. Interstitial techniques in addition to external beam therapy have also been advocated (2).

In Sweden, the first series of radical radiotherapy in mainly poorly differentiated prostatic carcinoma was reported by Edsmyr et al. (3).

The aim of the present study is to evaluate radical radiotherapy in patients with mainly poorly differentiated prostatic carcinoma with respect to tumour effects and side effects. The series includes 111 patients treated from 1978 to 1986.

## Material and Methods

During the years 1978–1986, a total of 1575 new cases of carcinoma of the prostate were diagnosed in the city of Malmö (total population approximately 235000). Out of these, 574 were found incidently at post mortem, making the number of clinical cases 1001. Out of these, 227 were referred for radiotherapy, which in 111 was planned to be radical. These 111 patients constitute the present series. Usually, only patients with undifferentiated or poorly differentiated, localized carcinomas were considered for radical radiotherapy.

The ages of the patients (Table 1) ranged from 50 to 85 with a median of 71 years, and the patients were thus relatively elderly. Table 1 also gives the fraction of all reported patients with a clinical diagnosis of prostatic carcinoma in the different age intervals, who received radical radiotherapy. Such therapy was most frequent in the 60–64 age group.

In 50 patients the diagnosis was based on fine needle aspiration biopsy according to Franzén et al. (4) and cytological evaluation only. Three patients had had an enucleation, and in the remaining 58 patients the cancer diagnosis was made by transurethral resection of the prostate. In this group of resected patients 32 also had a

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positive fine needle aspiration biopsy, whereas in 8 patients this procedure was negative. A further 5 patients were reoperated upon, and in 2 patients a third operation was performed.

All microscopic slides were reviewed without knowledge of the clinical data. Of totally 105 fine needle aspirates from 90 patients, 103 could be retrieved and were reexamined and graded according to Esposti (5). All histological slides were reexamined and regraded according to Mostofi & Price (6) and in 56 patients the Gleason score (7) could be applied.

In all cases the cancer diagnosis was confirmed, and the regrading of the histological material was in concordance with primary diagnosis in 96% while regrading according to Esposti (5) was in concordance with primary diagnosis in 91%.

The grading was performed according to Mostofi & Price (6) when histopathological material was available and according to Esposti (5) when only cytological material was available. Ninety-nine of the 111 patients had poorly differentiated carcinoma, which represented an active selection criterium.

The staging procedure included physical examination, bone radionuclide scan, chest radiography, and routine blood tests including acid phosphatases. No staging lymphadenectomies were made.

Thirty-six patients were considered to have intracapsular carcinoma (stage B), whereas 75 were classified as extracapsular carcinoma (70 in stage C, and 5 in stage $D_1$) (8, 9). Nineteen had received oestrogens and 10 had been orchidectomized before radical radiotherapy.

For the radiotherapy (Fig. 1) typically 2 target volumes were identified, firstly the prostate and bladder (target I=full drawn lines in Fig. 1) and secondly the regional lymph nodes in the pelvis (target II=broken line in Fig. 1). As from 1980 a diagnostic CT-scan was usually available. Only one section was planned. The target doses aimed at were 68 Gy in target I and 44–50 Gy in target II. Typically (Fig. 1) a box-technique with four 43 MV photon beams from a betatron and an isocentric technique was used. One isodose plan was made for the treatment of targets I and II, and another for the 'boosting' of target I. The dose distribution in Fig. 1 represents the sum of 2 such different plans. Treatment with all beams was given at each fraction, and 5 fractions were given a week with daily target doses of 2.0 Gy. The mean (average) target dose was used for specification (10). In typical cases targets I and II received 44 Gy in 22 fractions over 26 days, and after a 3-week pause, the dose to target I was raised to 68 Gy in 34 fractions in 64 days (Fig. 1). The treatment geometry was set up at a simulator, and further checked by means of treatment verification films.

The patients were followed up regularly at the Departments of Oncology/Radiotherapy, and Urology with special emphasis on tumour status as well as side effects and complications. Fine needle aspiration biopsy of the prostate was not performed as a routine follow-up procedure. The end of follow-up for the present analysis was June 1987.

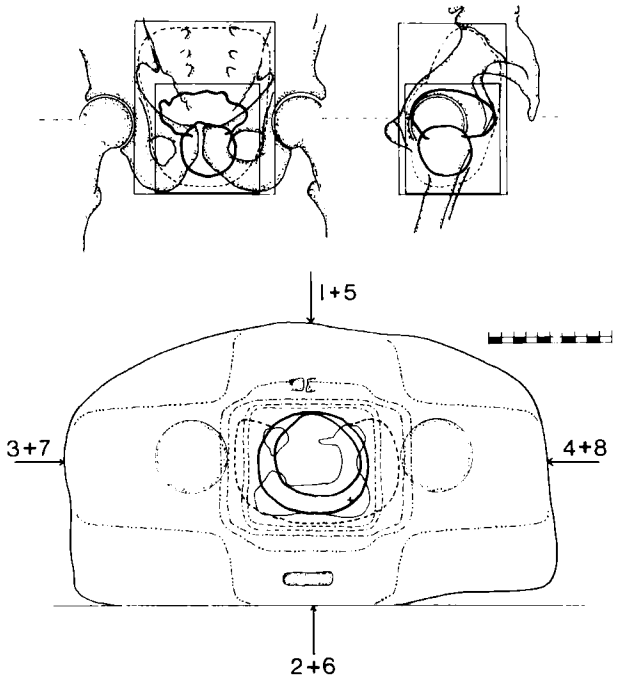


Fig. 1. Typical representation of the 2 target volumes (target I = prostatae and bladder, full drawn lines, and target II = regional lymph nodes, = broken line), dose plan showing total dose distribution, and field arrangement. 43 MV photons, isocentric technique. For further details, see text. *Field sizes:* 1&2=14.5×17.0 $cm^2$, 3&4=10.5×17.0 $cm^2$, 5&6=10.5×11.0 $cm^2$, 7&8=10.0×11.0 $cm^2$. *Value of isodose lines:* +=max. dose 69 Gy, —— = 68 Gy, ---·--- = 66 Gy, --·-- = 64 Gy, —·— = 50 Gy, —··— = 40 Gy, —···— = 20 Gy.

**Table 1**

*Age distribution of 111 patients. The percentage figures give the fraction of all patients in Malmö with a clinical diagnosis of prostatic carcinoma in each age interval, who were accepted for radical radiotherapy*

| Age interval (years) | No. of patients (%) |
|---|---|
| <50 | 0 |
| 50–54 | 1 (11) |
| 55–59 | 6 (17) |
| 60–64 | 23 (22) |
| 65–69 | 22 (14) |
| 70–74 | 25 (11) |
| 75–79 | 20 (9) |
| 80–84 | 13 (9) |
| 85–89 | 1 (1) |
| >89 | 0 |

## Results

The pooled cytological and histopathological evaluation (5, 6) showed that one patient (1%) had well differentiated, 10 (9%) moderately well differentiated, and 99 (89%)

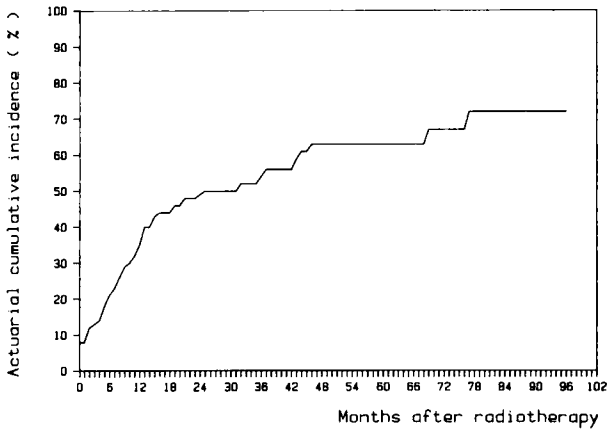


Fig. 2. Cumulative actuarial incidence of relapse locally or at distant sites during follow-up.

**Table 2**

*Ninety out of the 111 patients who had different symptoms and signs of late effects probably (or possibly) due to radiation. Totally for each side effect, and, for some of the reactions, subdivided into different grades of severity seriousness. For explanation, see text*

| | No. of patients | | | |
|---|---|---|---|---|
| | Totally | Subdivided on different grades of side-effects | | |
| | | 1 | 2 | 3 |
| Bladder | | | | |
| Irritable bladder | 42 | 17 | 18 | 7 |
| Haematuria | 16 | 12 | 3 | 1 |
| Urinary incontinence | 20 | 12 | 6 | 2 |
| Bladder contraction | 9 | | 6 | 3 |
| Urethral stricture | 3 | | | |
| Suprapubic catheter | 2 | | | |
| Nephrostomy due to urethritis | 3 | | | |
| Intestine | | | | |
| Diarrhea | 31 | 28 | 3 | |
| Meteorism | 4 | 4 | | |
| Fecal incontinence | 7 | 6 | 1 | |
| Tenesm, perianal pain | 5 | | 5 | |
| Proctitis | 33 | 20 | 11 | 2 |
| Pubic oedema | 5 | 4 | 1 | |
| Stenosis anii | 7 | | | |
| Sigmoideostomy due to proctitis | 2 | | | |
| Sepsis | 2 | | | |
| Fibrosis | 11 | | | |

poorly differentiated carcinoma. One tumour could not be graded. The vast majority of the 111 patients thus had grade 3 tumours, which usually was an inclusion criterion for the treatment. Due to this selection the present series was not suitable for an analysis of the possible prognostic influence of grading.

For 56 patients Gleason score (7) could be applied; 9 (16%) had score 5–6–7 and 47 (84%) score 8–9–10. Cytological grading according to Esposti (5) was performed in 78 patients and of these 6 (8%) had grade 1, 19 (24%) grade 2 and 53 (68%) grade 3 tumours.

Clinical staging according to Whitmore-Jewett (8, 9) revealed 36 patients (32%) with stage B (intracapsular carcinoma), 70 (63%) with stage C and 5 (5%) with stage D; 68% of the patients had thus extracapsular carcinoma.

Ninety-seven of the 111 patients received the prescribed radiation dose of 66–68 Gy, and 9 patients received 64 Gy. In the remaining 5, only doses in the range of 40–62 Gy were given due to progressive disease during treatment (n=3), or poor tolerance to irradiation due to high age (n=2, 82 and 85 years respectively).

Early radiation side effects (within 3 months), such as lassitude, proctitis, and bladder irritation, were noted in expected frequency and degree.

Late side effects (after at least 3 months), probably or possibly attributable to the irradiation, were subjected to a special analysis (Table 2). The observations were made during a total of 302 man-years' follow-up, whereof 248 man-years derived from patients followed at least 6 months. In 21 of the 111 patients, no such late side effects were noted, whereas 90 patients showed one or more of such reactions. The effects (Table 2) were referred to 3 different grades:

grade 1 = mild symptoms and/or signs, no necessitating constant treatment,

grade 2 = moderate symptoms/signs, necessitating constant special treatment, usually medication,

grade 3 = severe side effect, usually requiring surgical intervention, e.g. urinary deviation.

Thus, 19% of the patients did not show late radiation side effects, whereas the remaining 81% did (Table 2), and in 19% of these some form of surgical intervention was required.

Twenty-five of the patients had a catheter (KAD) during treatment. These patients often had different side effects during and after treatment, but since they had a KAD for a variety of reasons, which *per se* might have contributed to the side effects, it is not possible to state the exact role of the catheter.

Twenty-five patients had elevated values of acid phosphatases before therapy, which in 10 of them returned to normal. With the exception of 9 patients who progressed during treatment (see below), this series did not permit conclusions regarding the implications of elevated acid phosphatases.

At conclusion of therapy, 9 patients had developed distant metastases, and were considered primary failures (Fig. 2). All these 9 patients had steadily elevated acid phosphatases during treatment. During the follow-up, a local recurrence or distant metastases were diagnosed in an increasing number of patients. Actuarial analysis showed (Fig. 2) that at the end of the follow-up (at 8

**Table 3**

*Local tumour status and metastases in 54 deceased patients*

| | No. of patients | |
|---|---|---|
| | Post mortem | No post mortem |
| Tumour locally and metastases | 29 | 2 |
| Tumour locally, no metastases | 8 | 0 |
| Tumour locally, metastases not evaluable | 0 | 1 |
| Local tumour status not evaluable, metastases | 1 | 8 |
| Local tumour status not evaluable, metastases not evaluable | 0 | 2 |
| No local tumour, no metastases | 1 | 0 |
| No local tumour, metastases | 2 | 0 |
| Total | 41 | 13 |
| Para-aortic lymph node metastases | 24 | |

years), relapse locally or at distant sites had been recorded in 72% of the patients.

Fifty-four patients have died (Table 3). An autopsy was performed in 41, showing residual carcinoma in 37 and no local tumour in only 3 (one patient not evaluable). Thirty-three or the 41 deceased patients who underwent a post mortem had metastases. In 24 of the 41 were para-aortic lymph node metastases demonstrated, but this figure may be considered somewhat uncertain due to reporting variations in the post mortem records. Of 13 deceased patients who did not undergo a post mortem, local tumour was evident in 3 and metastases in 10, but in many of these 13 patients it was not possible to make any statements about tumour status. Thus, among the 54 patients who had died, local tumour was present in 40, absent in 3, and not evaluable in 11. Metastases had been demonstrated in 42, were absent in 9, and not evaluable in 3.

The actuarial survival is given in Fig. 3, as well as the expected survival for an age-matched Swedish male population. The actuarial 8-year-survival rate in the present series was 25%. This figure should be compared with 65% for an age-matched population. After 3 years the 2 survival curves (Fig. 3) became parallel, indicating an age-corrected 'cure'rate of the order of 49%.

The actuarial survival was significantly better for patients clinically judged to have only intracapsular tumours (stage B) than for those, judged to have extracapsular extensions (stages C and D) (Fig. 4) (p=0.01, generalized Wilcoxon's test).

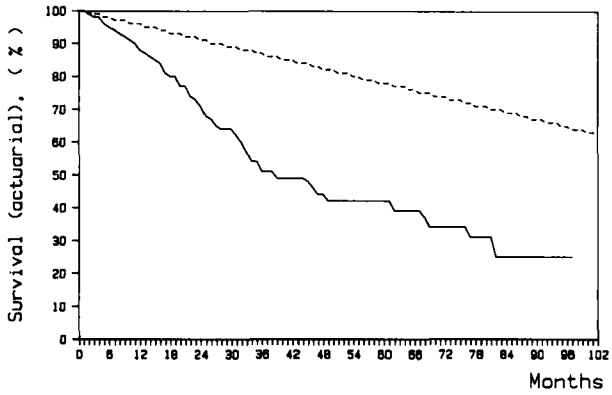


Fig. 3. Actuarial survival (——) of 111 patients. Also shown expected survival (· · · ·) of an age-matched Swedish male population.

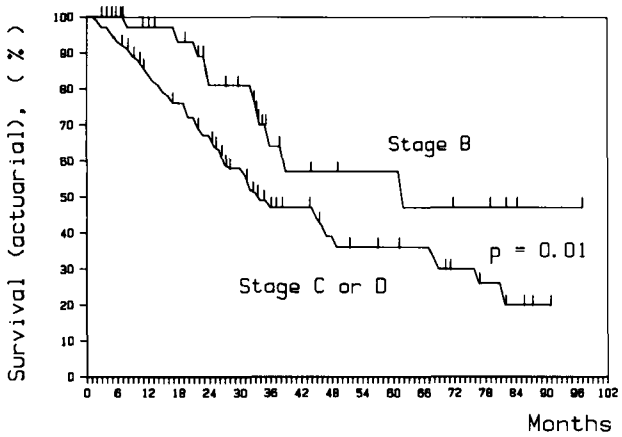


Fig. 4. Actuarial survival of 36 patients in stage B and 75 patients in stages C or D (Whitmore & Jewett) (8, 9). The difference is significant (p=0.01) (generalized Wilcoxon-test). The vertical bars indicate the length of follow-up for censored patients.

Only 9 patients had Gleason scores of 5–6–7, and out of these 7 had extracapsular disease, and only 2 had intracapsular disease. The actuarial survival rate for these few patients with Gleason scores of 5–6–7 was 47% at 36 months (the survival NED = 54% at 36 months), which is not different from the figures for the whole series of 111 patients.

Concerning the 78 patients with cytologically graded tumours according to Esposti (5), the proportion of patients judged to have extracapsular disease was 66%, 58%, and 70% for grades 1, 2, and 3 respectively. Thus no large differences were seen in this respect between the different grades. Fig. 5 gives the actuarial survival and the actuarial survival NED for patients cytologically graded according to Esposti. All 6 patients with grade 1 were censored alive and NED during a follow-up of at most 92 months. Otherwise, the different grades did not predict survival or survival NED, and actually, after 3 years patients with grade 3 fared better than the few patients

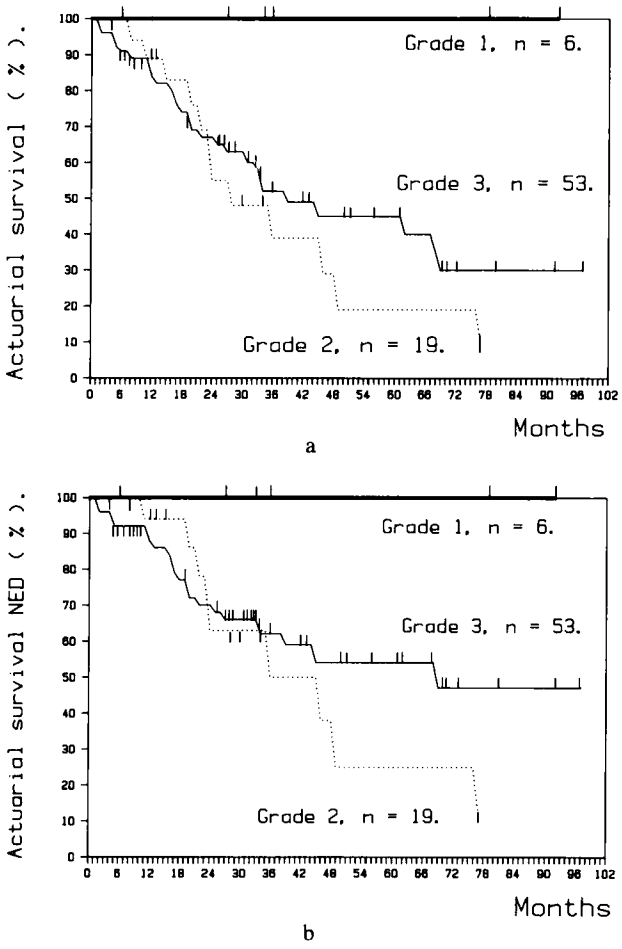


Fig. 5. Cytological grading in 78 patients according to Esposti (5). For 3 different grades are given actuarial survival (upper) and actuarial survival NED (lower). The vertical bars indicate 38 patients who were censored alive (upper) and 48 patients who were censored alive or dead NED (lower).

with grade 2. However, the present patient series was, as mentioned previously, highly selective with regard to grading when the therapy was decided, and the role of this, with respect to the findings in Fig. 5, is unclear.

## Discussion

It seems obvious that the extent of local tumour spread is of great prognostic importance. The TNM classification (11) is often considered to be somewhat unpractical, and most reports use the Whitmore-Jewett system (8, 9). In large series, many patients (at least 60%) with only intracapsular disease are reported to have a long-term survival after radical radiotherapy, whereas only approximately 20% of those with extracapsular extension are alive after 15 years (1). Even higher survival rates for the different stages, being of the order of 80–100% for stages A and B, 60–90% for stage C, and 40% for stage $D_1$, have been reported (12, 13) in mainly well or moderately well differentiated tumours.

The microscopic grade of the tumours, usually defined according to Mostofi & Price (6), or Esposti (5), have also been shown to be of great prognostic importance (14, 15), the long-term survival rate after radical radiotherapy being approximately 4 times higher for patients with well differentiated tumours than for those with poorly differentiated ones (14). In a series (16) of patients treated with radical radiotherapy for mainly well or moderately well differentiated stage C tumours, the crude 10-year-survival rate was approximately 47%, which corresponded to the figure 70% when age-corrected. The figure is better than the one found in the present series, and points to the importance of grade. It also stresses the need for correction for age when reporting survival rates in these often relatively aged patients.

Other methods of microscopic classification, which particularly take into account the type of invasive growth and its relation to the normal tissues, such as the Gleason scoring system (7) have been shown to correlate significantly with prognosis (1, 17).

In a RTOG-study of 566 evaluable patients, Pilepich et al. (18) analysed possible prognostic factors, including tumour size, clinical stage, degree of histological differentiation, nodal status, serum acid phosphatase status, hormonal management status, age, and race. In a correlation study between the assessed variables and the used endpoints (local control, incidence of distant metastases, NED survival, survival), the degree of histological differentiation turned out to be the most powerful prognostic factor.

Edsmyr et al. (3) reported a 67% 2-year-survival rate, which is of the same order as that found in the present series.

Approximately 20–25% of patients with stage $A_2$ (8, 9) and B and approximately 50% of patients with stage C can be expected to have lymph node involvement which could be proved by staging lymphadenectomy (17). Evaluation of the presence or absence of regional lymph node metastases may then be an important issue. Regarding the lumbar lymph nodes, their inclusion in the target volume has not improved the results compared to pelvic irradiation alone (12, 17).

In a PCS (patterns of care study), Hanks (19) made an analysis on the radiation dose that might seem optimal. The frequency of a local relapse at 4 years decreased from approximately 24% at doses below 55 Gy to approximately 10% at doses of 70 Gy or more.

The relatively large target volumes and high radiation doses that are used carry a significant risk of pronounced side effects and complications. Thus, Edsmyr et al. (3) reported on 3 complications in 23 patients given 55 Gy in 5–7 weeks together with oestrogens. Several papers report in detail on the side effects and complications of radiotherapy (12–14, 16, 19). The frequency of major com-

plications ranges from 4 to 16%, and that of pronounced early side effects is usually of the order of 25%. Loss of potency is reported to occur in 5–13%. Symptoms secondary to bladder and rectal injuries have, however, been reported to be reversible in over 50% of the patients within the first year of onset (20).

In a pooled series of patients from different centres, Pilepich et al. (21) reported that in patients with stage $A_2$ or B disease, staged by means of staging lymphadenectomy, bone scan, and of serum acid phosphatase, there was a low (less than 10%) probability of progression (distant metastases) within the first 5 years. Contrary to a report from the VA uro-oncology-group (22) the pooled results in the Pilepich-series indicated that the outcome should be comparable in radiation treated and surgically treated patients. This problem, however, is still open to be investigated. Pilepich et al. (21) in an analysis of the Paulson-report (22) found that they could not assess the possible implications of e.g. moving patients between the 2 treatment arms after randomization.

The present series consists of a fairly elderly group of patients. Almost all had poorly differentiated carcinoma, and two-thirds had clinically extracapsular extension of their tumours. The survival should then be rather poor. The projected 8-year survival was 25%, and should be compared with the expected figure of 65% for an age-matched male population. After 3 years, the 2 survival curves became rather parallel, indicating a 'cure' rate of the order of 49%. The survival was significantly better for patients judged to be in stage B than for those in stage C and D. During the follow-up 72% of the patients (actuarial analysis) developed relapse locally or at distant sites. This high figure probably reflects the biology of poorly differentiated prostatic carcinoma. In a relatively large proportion of the deceased patients a post mortem examination was performed, and most of these had tumour locally as well as distantly.

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