

# External Beam Radiation Therapy of Adenocarcinoma of the Prostate

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## ABSTRACT

The record of radiation therapy cases during a five year period at the University of Michigan Hospitals has been analyzed. Of a total of 73 adenocarcinoma of prostate, the majority belonged to Stage B and C which represented 49 and 20 cases, respectively. The mortality rate after irradiation was clearly related to the tumor stage. Local irradiation resulted in 88% of the local control of well-differentiated adenocarcinomas. Stage C cases had 50% mortality, whereas that of Stage B patients was 14%. Results of this study are in general agreement with previous data in terms of the local disease control after irradiation and provide a basis for conservative radiotherapy regimen as an approach in the treatment of localized prostatic carcinomas.

## INTRODUCTION

Carcinoma of the prostate, a major cause of morbidity and mortality among older men in the United States, is responsible for almost 20,000 deaths annually. Since the limitations of endocrine therapy became clear in the 1950's, aggressive radiotherapy of prostatic carcinomas gained renewed appeal, particularly as the new equipment for external irradiation with large doses have become available<sup>1,2</sup>. Within the past several years

a number of articles<sup>1,2,7,8</sup>) and a review article<sup>11</sup>) have been reported from different groups, but more data is needed to develop a generalized theoretical basis and treatment plans for the varied forms of prostatic carcinomas.

At the University of Michigan Hospitals, prostatic carcinomas have been treated using a uniform therapeutic approach throughout the years, largely because of the pioneering efforts and leadership provided by the late Dr. Isadore Lampe. This article reports the results obtained from our recent review of prostatic carcinoma cases over a five-year period.

## MATERIAL AND METHOD

This paper reviews 80 male patients who were treated with curative external beam teletherapy for histologically proven carcinoma of the prostate between 1970 and 1975 at the University of Michigan Hospitals, Ann Arbor, Michigan. They were followed for a minimum period of 5 to 10 years. Four patients were lost during the follow-up program and they have been eliminated from this paper. There were 73 cases of adenocarcinomas, one squamous cell carcinoma, one transitional cell carcinoma and one sarcoma. For this study only adenocarcinoma of the prostate was reviewed.

The distribution of age in the study population was 45 to 84 with an average age of 66.3. In 80% of the patients, tumor was diagnosed within

**Table 1. Symptoms and Signs among Prostatic Carcinoma Cases**

| Symptoms and Sign    | Present | Absent | Unknown |
|----------------------|---------|--------|---------|
| Obstruction          | 52      | 12     | 9       |
| Nocturia(3-5 x)      | 30      | 4      | 39      |
| Increased frequency  | 27      | 9      | 37      |
| Urinary incontinence | 11      | 7      | 55      |
| Potency              | 6       | 1      | 57      |

3 months prior to the initiation of radiation therapy.

There were 25 cases of cardiac disease, 17 hypertension cases, 9 obese and 7 diabetic patients. There were 3 concurrent neoplasms and 4 cases of previous neoplasm. Table 1 records symptoms and signs observed in these patients at the time of diagnosis. The majority of the case (52) had obstructive symptoms. Among the other 30 cases observed, 3 to 5 times of nocturia of greater frequency and 11 cases shown urinary incontinence. There were 63 white, 9 black and one Asian patient. There were 61 patients diagnosed by transurethral resection of prostate and 12 patients by needle biopsy. IVP was performed in all patient prior to the treatment. There were 10 abnormal cases and 63 with normal IVP. Acid phosphatase activity indicated 43 normal cases, 4 cases showing an increase of less than 2 times the normal level and 2 cases of more than 2 times the normal value. The enzyme activity was undetermined in the remaining 24 cases.

Cystoscopy was performed in 65 cases; one showed elevated trigone and 3 cases demonstrated a bladder invasion. The patients were staged

according to the following classification: Stage A—carcinoma of multiple foci incidentally found in a prostatectomy specimen usually for benign hyperplasia; Stage B—multiple palpable nodules within the capsule of the prostate; Stage C—extracapsular invasion or extension into the seminal vesicles and bladder; and Stage D—evidence of metastasis outside the pelvis.

There were 4 patients staged as A (6%), 49 staged as B (67%) and 20 staged as C (27%) (Table 2). Fifty-five patients (75.3%) had not received previous treatment; 18 patients (24.7%) had received previous treatment, including one surgical, 15 hormonal and 2 multi-disciplinary treatments. Of the 18 patients with previous treatment there were 2 cases of Stage A, 11 of Stage B and 5 of Stage C.

Among the 15 cases who received hormonal treatments, 3 were orchiectomized, 7 were given hormone alone and 5 received both treatments. Twenty-seven patients were referred to us from the University of Michigan Hospitals, 43 by urologists in the neighboring community, and three were unclear. All biopsy specimens were reviewed by our pathologists. Table 2 demonstrates the relationship between clinical stages and histologic grades in prostate carcinoma. There were 34 cases of well-differentiated adenocarcinoma of the prostate.

All patients during this period were treated with Cobalt 60 teletherapy with 360° rotation. Anteroposterior and lateral radiographs were taken to define the tumor volume. Figures 1 and 2 are examples of radiographs illustrating AP and

**Table 2. Relationship between Clinical Stage and Histologic Grade in Prostatic Carcinoma**

| Stage    | Histological Grade  |                           |                       | Total |
|----------|---------------------|---------------------------|-----------------------|-------|
|          | Well Differentiated | Moderately Differentiated | Poorly Differentiated |       |
| A        | 3                   | 1                         | 0                     | 4     |
| B        | 24                  | 19                        | 6                     | 49    |
| C        | 7                   | 9                         | 4                     | 20    |
| Total(%) | 34(46)              | 29(40)                    | 10(14)                |       |

lateral treatment fields. The representative isodose distribution is shown in Figure 3. In the majority of cases the field size was 12×12 cm, (ranging 10 to 14 cm) which included 90% contour of the prescribed dose. The number of treatments was 33 (ranging 32 to 36). The total number of treatment

periods averaged 47 days (ranging from 44 to 58) with a schedule of five daily treatments a week. Total dose was 6530 rads (ranging from 6320 to 6646 rads).

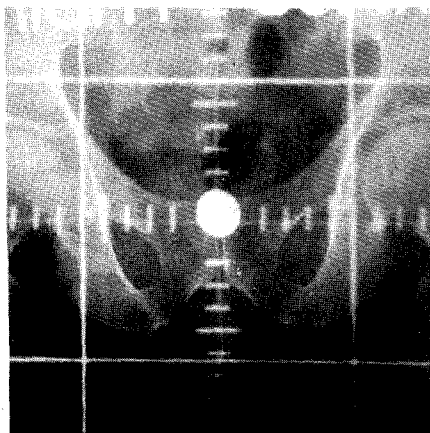


Fig. 1. Anterior-posterior radiograph showing treatment volume. Note the mercury-filled Foley catheter which denotes the position of the prostatic urethra.

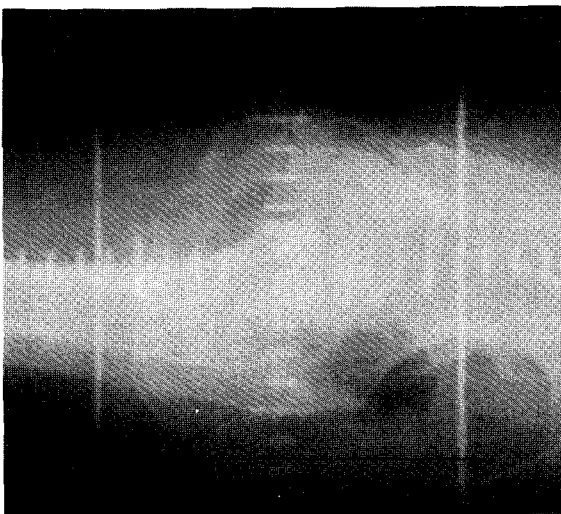


Fig. 2. Lateral radiograph showing treatment volume. Note the mercury filled Foley catheter which denotes the position of the prostatic urethra.

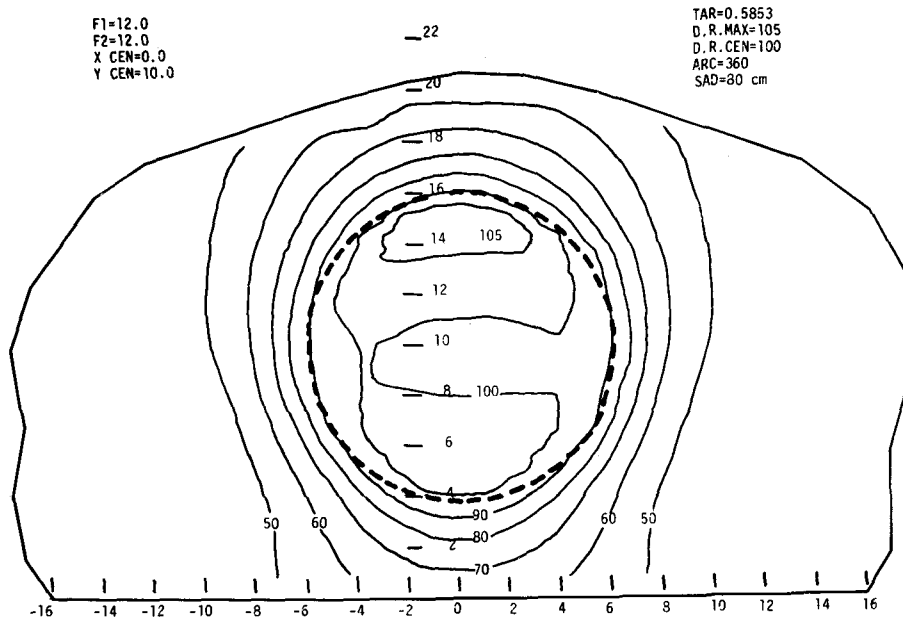


Fig. 3. Isodose distribution for treating carcinoma of the prostate with Cobalt 60, 360° rotation. Abbreviations: TAR-Tissue Air Ratio, D.R. MAX-Maximum Relative Dose Rate, D. R. CEN-Central Relative Dose Rate, F1-Field 1, F2-Field 2, SAD-Source Axis Distance.

## RESULTS

### Survival

Table 3 indicates results of the radiation treatment and the patient status relative to the stages of disease. None of the Stage A patients died with disease during this follow-up period. Seven patients of Stage B (14%) died with disease (average survival of 32.3 months, ranging between 14 and 81 months), and 10 cases of Stage C (50%) died with disease (average survival of 45.5 months, ranging 3 to 19 months). In total, 23% of carcinoma of the prostate cases died with disease during the 5 to 10 year follow-up period (average survival of 73.5 months with a range of 3 to 120 months).

The relationship between the histological grade of tumors and the clinical status of patients after radiation treatments, and the presence or absence

of local control are recorded in Tables 4 and 5, respectively. Out of 34 patients with well-differentiated adenocarcinoma of the prostate, 3 died with disease (8%) and 5 patients were alive with disease. In Table 5, local primary control was observed in 30 patient (88%) with well differe-

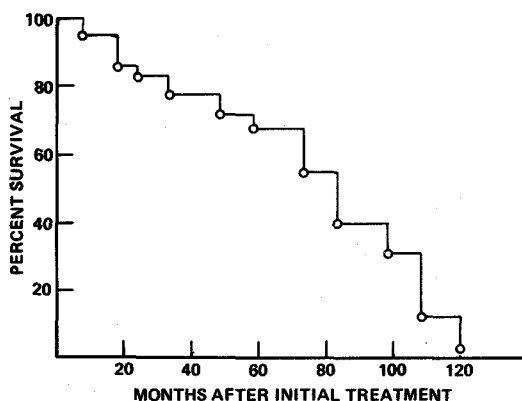


Fig. 4. Actual survival by the Kaplan and Meier method for 73 patients treated with radiation therapy.

Table 3. Relationship between Clinical Stage and Status after Radiation Treatment in Prostatic Carcinoma

| Stage    | Status After Radiation Therapy |                  |                 | Total |
|----------|--------------------------------|------------------|-----------------|-------|
|          | NED <sup>a</sup>               | Alive with Tumor | Died with Tumor |       |
| A        | 2                              | 1                | 0               | 4     |
| B        | 22                             | 9                | 7               | 49    |
| C        | 3                              | 6                | 10              | 20    |
| Total(%) | 27(37)                         | 16(22)           | 17(23)          | 73    |

<sup>a</sup> No evidence of disease.

<sup>b</sup> Intercurrent disease.

Table 4. Relationship between Histologic Grades and Post-Radiation Status in Prostatic Carcinoma

| Status After Radiation     | Histological Grade  |                           |                       | Total(%) |
|----------------------------|---------------------|---------------------------|-----------------------|----------|
|                            | Well Differentiated | Moderately Differentiated | Poorly Differentiated |          |
| NED <sup>a</sup>           | 20                  | 6                         | 1                     | 27(37)   |
| Alive with Disease         | 5                   | 9                         | 2                     | 16(22)   |
| Died with Disease          | 3                   | 8                         | 6                     | 17(23)   |
| Died with ICD <sup>b</sup> | 6                   | 6                         | 1                     | 13(18)   |

<sup>a</sup> No evidence of disease.

<sup>b</sup> Intercurrent disease.

**Table 5.** Relationship between Histologic Grades and Presence or Absence of Local Control in Prostatic Carcinoma

| Local Control | Histologic Grade    |                           |                       | Total(%) |
|---------------|---------------------|---------------------------|-----------------------|----------|
|               | Well Differentiated | Moderately Differentiated | Poorly Differentiated |          |
| Present       | 30                  | 20                        | 7                     | 57(78)   |
| Absent        | 4                   | 7                         | 3                     | 14(19)   |
| Unknown       | —                   | 2                         | —                     | 2( 3)    |

**Table 6.** Relationship between Local Control and Post-Radiation Status in Prostatic Carcinoma

| Post radiation Status      | Results of Treatment |                    |                           |
|----------------------------|----------------------|--------------------|---------------------------|
|                            | Local Controlled     | Local Uncontrolled | Undetermined <sup>c</sup> |
| NED <sup>a</sup>           | 27                   | 0                  | 0                         |
| Alive with Tumor           | 10                   | 4                  | 2                         |
| Died with Tumor            | 7                    | 10                 | 0                         |
| Died with ICD <sup>b</sup> | 13                   | 0                  | 0                         |
| Total(%)                   | 57(78)               | 14(19)             | 2(3)                      |

<sup>a</sup> No evidence of disease.

<sup>b</sup> Intercurrent disease.

<sup>c</sup> Undetermined cases.

**Table 7.** Relationship between Previous Treatment Status and Post Radiation Local Status

| Post Radiation Local Status | Previous Treatment status |         |
|-----------------------------|---------------------------|---------|
|                             | Untreated                 | Treated |
| Controlled                  | 45(82%)                   | 12(66%) |
| Uncontrolled                | 8                         | 6       |
| Undetermined                | 2                         | 0       |
| Total                       | 55                        | 18      |

the local control of the tumor. The relationship between post-radiation status and local control among the patients studied is shown in Table 6. A total of 57 out of 73 patients (78%) showed a local control, whereas 14 (19%) showed local failure. Furthermore, out of 17 patients who died with disease, 7 patients died without evidence of a local recurrence. Figure 4 records the overall survival of 73 patients. Among them, the actual 5 year survival is 68%. The mean survival length is 73.5 months (ranging 3 to 129 months). The

difference in survival curve between well to moderately differentiated tumor and poorly differentiated cases is depicted in Figure 5. Note the separation of the two curves between 30 and 110 months, suggesting that poor histological characteristics might be related to a prognosis of lower survival during intermediate periods after radiotherapy (about 3 to 9 years), whereas histologic difference is relatively unimportant after 10 years of treatment. Similarly 5 year survival of Stage B and Stage C was 87% and 83% respectively.

Out of 55 patients who had no previous treatment, 45 patients (82%) showed local control. However out of 18 patients who had previous treatment, either hormone or surgery, 12 (66%) patients showed local control (Table 7). Table 8 demonstrates that 23 out of 55 (42%), previously untreated patient, showed no evidence of disease and 8 (15%) died with tumor. However among 18 patient who had previous treatment prior to definitive radiation therapy only 4 (22%) patients

ntited tumor. However, 8 and 6 cases of moderately and poorly differentiated tumors (27% and 60%) died with disease, respectively. It is noteworthy that 3 out of 10 patients with poorly differentiated tumor (30%) showed a failure of had no evidence of disease and 9 (50%) patient died with tumor.

### Complications

There were 20 patients with post-radiation complications (Table 9). Among them, 11 cases presented with rectal symptoms involving rectal hemorrhage, stricture of the rectum and vesicorectal fistulae. Nineteen cases of urinary problems were noted. These included hemorrhagic cystitis, deep perineal pain, urethral stricture and 2 vesico-

rectal fistulae which required surgical intervention. The discrepancy between the number of patients (20) and that of complications (28) reflects the fact that some patients had both rectal and urinary problems. Other than the rectal hemorrhage cases which had an average latency period of 5 months after radiation, most other complications appeared between 1 and 2 years after the treatment.

### Metastasis

Metastasis subsequent to radiation treatment were found in 16 cases: 10 cases in bone, one case of lymph nodes beyond regional nodes, two cases involving both bone and nodes, and three cases of lung and bone. These cases were given further

Table 8. Relationship between Previous Treatment Status and Post Radiation Status

| Post Radiation Status | Previous Treatment Status |          |
|-----------------------|---------------------------|----------|
|                       | Untreated                 | Treated* |
| NED                   | 23                        | 4        |
| Alive with Tumor      | 12                        | 4        |
| Died with Tumor       | 8                         | 9        |
| Died with ICD         | 12                        | 1        |
| Total                 | 55                        | 18       |

\*Hormone or Surgery

Table 9. Nature of Post-Radiation Complications and Time of Their Appearance

| Symptoms             | Number of Case | Average Duration Between Treatment and Occurrence (Range in Month) |
|----------------------|----------------|--|
| Hemorrhagic Cystitis | 7              | 23.4(3~36)   |
| Rectal Hemorrhage    | 6              | 5.0(1~9)   |
| Deep Perineal Pain   | 6              | 16.7(10~30)  |
| Urethral Stricture   | 4              | 14.5(8~21)   |
| Rectal Stricture     | 3              | Unknown  |
| Vesicorectal Fistula | 2              | 23.0   |

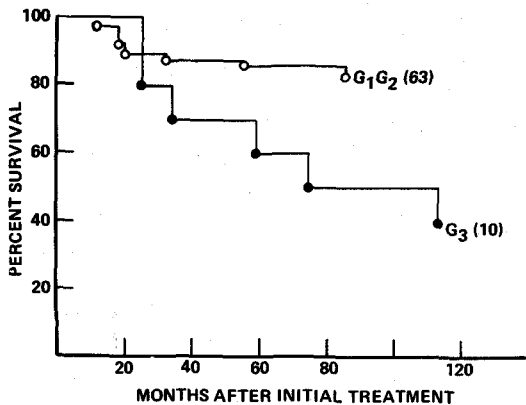


Fig. 5. Actual survival by the Kaplan and Meier method for patients with prostatic carcinoma according to histological differentiation of the tumor (G1, G2 and G3).

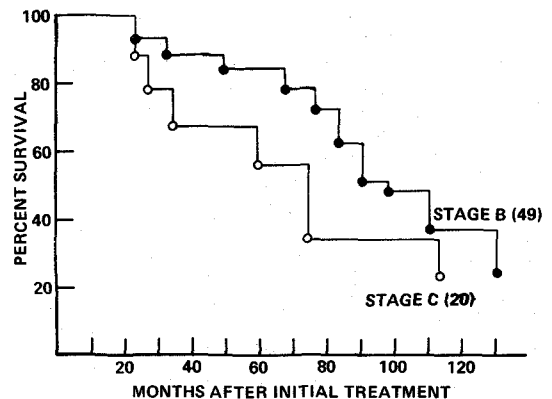


Fig. 6. Actual survival by the Kaplan and Meier method for patients with prostatic carcinoma according to Stage B and C.

treatment as follows: two cases were irradiated for bone metastasis; ten cases with bone and nodal metastasis were given hormonal treatment; the remaining cases were treated with chemotherapy or with chemotherapy and radiation therapy. The average interval between the primary treatment and the presentation of metastasis was 44.5 months (a range of 6 to 111 months)

## DISCUSSION

Rapid technological changes and the particular practice pattern of a given regional area makes it difficult to compare therapeutic records of the past with that which is being done today. Computed tomography (CT scan) was not available during the period of study reported in this article. Lymphangiogram was available during the late 1960's and early 70's, so only a few cases included lymphangiographic records. The reason that the majority of the cases treated did not have this diagnostic regimen was because they represented referral cases by local practitioners who had already given a diagnosis that was satisfactory to this department.

The field of radiation therapy employed during the period reported does not encompass all pelvic lymph nodes. Our treatment plan has used a radiation portal size comparable to those used by Bagshaw, et al.<sup>13</sup> and Perez, et al.<sup>8</sup> who reported local control percentages of 80% and 82% respectively. The result of our analysis indicates a local control of 78% of the cases. Thus, there seems to be a general agreement with respect to the local control and treatment field size employed at the three different institutions. These results were observed after localized treatments of the prostate and periprostatic region without any specific attempts to cover pelvic lymph nodes. The high survival rate obtained by localized therapy in these studies provides a persuasive basis for a conservative and limited approach to radiation therapy. An increase of the irradiated volume has failed to show an improvement in survival at 5

years.<sup>4,5</sup> However, this conclusion should be taken as a tentative one, inasmuch as it is somewhat contrary to theoretical expectations. Further observations in the future are needed to either confirm or refute this position.

Mortality of the treated patients appears to be clearly related to the tumor stage as evidenced by 50% mortality of Stage C cases (10 out of 20) as opposed to 14% mortality of patients with Stage B carcinoma (7 out of 49) with respect to the histologic picture of the tumors. The poor prognosis for Stage C cases with poor histologic differentiation supports the previously published data.<sup>1,3,5-8,10</sup> The patients being treated previously with hormone and/or surgery showed poor overall survival and lower local control rate than untreated cases (Table 7 & 8).

The complications recorded in this report represent observations of clinical symptoms that had developed over a long period of time, and majority of cases required conservative measurements. It is of interest that our records do not indicate any persistent, severe cases of gastrointestinal problems of the type previously described.<sup>3,9,10</sup>

## CONCLUSION

The study of 73 prostatic adenocarcinoma cases treated over a five-year period at the University of Michigan Hospitals indicated the following:

- 1) The majority of the cases belonged to Stages B and C, which represented 49 and 20 cases respectively.
- 2) The mortality rate after irradiation was related to the stage of the disease.
- 3) Local irradiation resulted in 78% of local control.
- 4) The overall consideration of this study confirmed the view that conservative radiotherapy might be a preferred approach to the treatment of localized prostatic carcinomas.

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