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Therapeutic Options for Localized Carcinoma of the Prostate: The Role of External Beam Radiation Therapy

Mark S. Khil, MD,* and Jae Ho Kim, MD, PhD*

During the last three decades the use of ionizing radiation, both external beam radiotherapy and interstitial radionuclide implant (brachytherapy), has greatly increased for the treatment of cancer of the prostate. The increased use of radiation therapy is in part due to the technological advance of high-energy megavoltage units as well as the steadily improving long-term results of radiotherapy. Because of the comparable tumor control rates, patients with early stage prostate cancer have several therapeutic options for curative treatment including radical prostatectomy, external beam radiation therapy, and interstitial brachytherapy. The role of external beam radiotherapy is discussed in terms of the primary management of early and locally advanced prostate cancers as well as the treatment of residual or recurrent disease after prostatectomy. A new approach combines antimitotic chemotherapeutic agents and radiation therapy for the treatment of locally advanced cancers of the prostate. (Henry Ford Hosp Med J 1992;40:103-7)

Prostate cancer is the second most common malignant disease in American men, and the incidence increases each decade after the age of 50. Approximately 122,000 new cases of prostate cancer were expected to be diagnosed in 1991. Although 60% of these patients will have localized disease, 32,000 deaths are predicted (1).

The use of ionizing radiation in the treatment of adenocarcinoma of the prostate, both by external beam (teletherapy) and by interstitial implant (brachytherapy), has greatly increased during the last three decades. Of more than 200 patients with cancer of the prostate seen annually in our department, over 50% are being evaluated for definitive radical radiation therapy for localized disease. Our purpose is to review this treatment and to emphasize the possibility of cure with external beam radiotherapy.

Historical Perspective

Reports of external beam radiation therapy from the 1930s through the 1950s dealt mainly with results obtained with orthovoltage (250 KVP) radiation (2,3). This treatment delivered maximum energy in the skin and subcutaneous tissues with excessive scattering of radiation; the delivery of a tumoricidal dose to the prostate was not always possible without unacceptable damage to the skin and surrounding normal tissue. Despite these limitations, Smith and Pierson (4) and Widmann (5) reported relatively good results in the relief of pain associated with bony metastases, and the latter presented impressive results in 82 cases with advanced local neoplasm treated for palliation of symptoms. All forms of treatment were eclipsed in 1941 when Huggins et al (6) showed that the growth of prostatic carcinoma could be retarded by androgen deprivation. Later, however, as the limitations of hormonal treatment became apparent,

interest renewed in the radiotherapeutic management of the disease. In 1952, Flocks et al (7) at the University of Iowa showed that the instillation of a short-lived radionuclide, gold colloidal suspension (^{198}Au), directly into the neoplasm and/or periprostatic soft tissues following subtotal resection decreased the local recurrence rate.

The use of ionizing radiation, stimulated by the report of Flocks et al, and the development of a high-energy megavoltage x-ray machine prompted renewed interest in the possible use of external beam radiotherapy. The availability of new megavoltage radiation therapy units ($> 1 \text{ MeV}$) allowed the delivery of a high tumoricidal dose to the prostate without excessive damage to the adjacent normal tissues—skin, subcutaneous tissues, and bones. In 1962 Bagshaw and Kaplan (8) at Stanford University presented their observations on the application of external beam irradiation as definitive treatment for carcinoma of the prostate. This was followed in the next two decades by other reports which attested to the radiocurability of carcinoma of the prostate and the feasibility of definitive treatment by external beam megavoltage irradiation.

Therapeutic Options for Early Stage Prostate Cancer

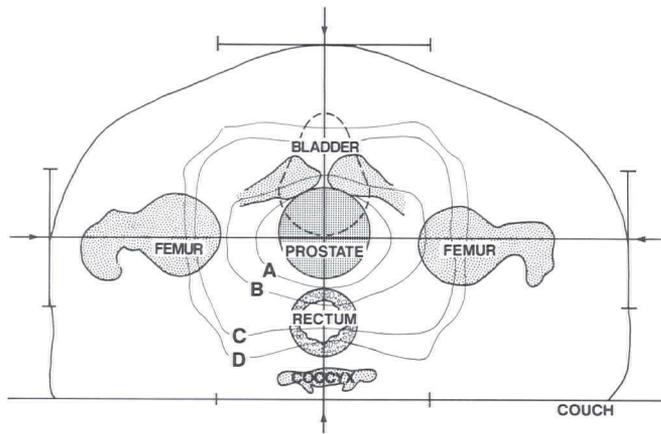
Although many urologic oncologists agree that patients with locally advanced prostatic cancer (stages B2 and C) may be best treated with definitive external beam radiation therapy, the use of radiotherapy in the treatment of early stages of disease (i.e.,

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Figure—Isodose distribution of the radiation dose, taken at the level of the prostate (A, B, C, D represent an isodose line of 6,600 cGy, 6,400 cGy, 5,000 cGy, and 4,000 cGy, respectively).

A2 and B1) has been less well defined. Radical prostatectomy is a well-established therapy for early localized prostate cancer. In particular, patients with stage B1 cancer with low-grade histology (e.g., Gleason score of less than 6) are the ideal group for radical surgery. If patients are not candidates for radical surgery for either medical or other reasons, they are eligible for radical radiation therapy. Such patients are then evaluated for either radioactive interstitial implant or external beam radiation therapy.

Radionuclide brachytherapy offers several advantages over external beam radiation therapy. These include 1) delivery of a high local dose to the prostate over several months, 2) limited injury to the adjacent organs because of the geometric fall-off of the radiation dose with distance from the seeds as well as attenuation by tissue, 3) completion of therapy at one setting, and 4) the opportunity at the time of implantation to stage the disease accurately by bilateral pelvic lymphadenectomy. Indications for radionuclide brachytherapy (e.g., iodine-125 or palladium-103) are usually comparable to those for a radical prostatectomy (i.e., patients with stage B1 or B2 with low-grade histology). In recent years, substantial progress has been made to improve distribution of the radiation dose within the prostate using computed tomography (CT) or transrectal ultrasound to guide implantation. These approaches are technically far superior to conven-

tional retropubic implantation (9-15). We have successfully treated several early stage prostate cancers with a perineal implantation technique using CT-based guidance.

Most patients with early stage prostatic cancers (i.e., stages A2, B1, and B2 with high-grade histology) are excellent candidates for external beam radiation therapy. A high-energy external beam is essential to deliver the dose of radiation needed to achieve tumor control and to minimize damage to the adjacent normal tissue. External beam treatment of prostate cancer must involve a high-energy linear accelerator (usually more than 10 MeV x-rays), the use of simulation, and complex field arrangements (usually four or more fields), as well as optimization in the radiation dosimetry. CT scan and other imaging data are used to achieve this optimized treatment plan (Figure). The complex multiple field technique permits delivery of a curative dose of radiation (65 to 70 Gy) to the prostate with a minimal normal tissue morbidity.

The results of several large retrospective series (16-18) reporting external beam radiotherapy of the prostate cancer are presented in Table 1. Survival rates for treated patients with stage A disease at 5 and 10 years are 82%-95% and 70%-85%, respectively. Of patients with stage B tumors, 75% survived 5 years and 40% to 55% survived 10 years. Through 15 years of follow-up, overall survival in the patients treated surgically (19,20) and those in stage B1 treated with external beam radiotherapy (16) did not deviate significantly from each other (rates of 51%, 57%, and 52%, respectively).

Perez et al (17) reported a 70% disease-specific 10-year survival rate for stage A2 and 55% for stage B disease. The 10-year disease-specific rates in the patterns of care studies (PCS) in the United States are comparable (77% for stage A and 40% for stage B) (18).

Treatment of Locally Advanced Prostate Cancer (Stage C, D1, or T3-T4)

In all the series of prostate cancer presented to the National Institutes of Health Consensus Development Conference (June 1987), the initial size or stage of the tumor at diagnosis was the most significant factor in predicting the outcome (21). In patients who presented with a palpable tumor extending outside the prostate (stages T3 and T4 or stage C), local recurrence rates

Table 1
Survival Results With External Beam Radiation Therapy
in Localized Disease (Stages A and B)

Series		Overall (Actuarial) Survival (%)			Disease-Specific Survival (%)		
		5 years	10 years	15 years	5 years	10 years	15 years
Bagshaw et al (16)	A	95	75	45	95	85	85
	B1	80	60	35	85	75	64
	B2	80	55	33	85	65	45
Perez et al (17)	A2	79	67		82	70	
	B	76	56		75	55	
Hanks et al (18) (POC)	A	83	62		84	77	
	B	73	46		66	40	

POC = Patterns of care studies in the United States.

were 25% to 40% and the probability of progression with distant metastases was 50% to 75% (21). In contrast to the results achieved from the management of stages A and B disease, 10-year survival after presentation with locally advanced prostate cancer is a disappointing 20% to 40% (22-25). The tumor control rate by radiation therapy is inversely proportional to the size of the tumor and higher doses are necessary for larger tumors (26). External beam radiotherapy can be applied to periprostatic extension of cancer that cannot be removed surgically (stage C). Doses exceeding 7,000 cGy are necessary to minimize local recurrences (27). A significant problem with these data is the inaccuracy of clinical staging without surgery; the local lesion may be misstaged and the lymph nodes understaged in the absence of lymphadenopathy.

Optimal management of locally advanced prostate cancer with pelvic lymph node metastases (stage D1 or T4) is a therapeutic enigma. Regional lymph node involvement worsens the prognosis, for the risk of distant spread in these patients is reportedly 75% to 80% (28). Accordingly, a broad range of treatments have been evaluated: early initiation of chemotherapy; the combination of radiotherapy with hormonal manipulation; and prostatectomy with interstitial irradiation. No preferred regimen has been defined, and detailed discussion of these modalities is beyond the scope of this review. Data concerning radiation efficacy in patients with lymph node involvement are scarce. However, Bagshaw (29) reported that 14% to 18% (depending on radiation portals) of patients survived for more than 5 years without evidence of cancer. In 1982 Paulson et al (30) evaluated 41 patients with surgical stage D1 disease who were treated with extended field radiation alone. A total of 32% were alive and disease-free at 60 months. Although recent data using a mixed beam (neutron/photon) regimen for patients with locally advanced (stages C and D1) carcinoma of the prostate have shown superior results to standard photon therapy (locoregional control at 5 years, 81% versus 60%), the study included a relatively small number of patients and the follow-up was relatively short (31).

In an effort to improve local tumor control and to increase the survival rates of patients with locally advanced prostate cancer, we devised a novel approach combining antimetabolic chemotherapeutic agents and external beam radiation therapy. Based on the growing understanding of the mechanism of action of antimetabolic agents (e.g., estramustine phosphate and vinblastine sulfate), we initiated a phase II study of concomitant administration of estramustine and vinblastine in combination with external beam radiation therapy. Radiobiological studies indicate that cells accumulated in the G2 phase due to the drug-induced mitotic block would be highly sensitive to fractionated radiation therapy, resulting in enhanced tumor cell kill. To date, the tolerance of patients to this regimen has been excellent.

Adjuvant Radiation Therapy After Prostatectomy for Pathologic Stage C Cancer

Postoperative radiotherapy has not been used so commonly for cancer of the prostate as for other cancers but has been used

Table 2
**Postprostatectomy Radiation Therapy
Before Local Recurrence**

Series	Number of Locally Controlled/ Number of Patients	Five-Year Survival (%)
Rosen et al (32)	15/16	94
Gibbons et al (33)	21/22	73
Hanks & Dawson (34)	10/10	86
Ray et al (35)	10/13	57
Pilepich et al (36)	18/18	45
Total	74/79 (94%)	

in small groups of patients at several centers. For the most part, this treatment has been utilized in patients after incomplete surgery or in those with pathologic stage C malignancy (surgical margin positive in histological examination, microscopic invasion through the capsule or infiltration of the seminal vesicles). In these patients, local recurrence would be expected in 20% to 45% after surgery alone. The local control of prostate cancer when adjuvant irradiation was given either before or after local recurrence is tabulated in Tables 2 and 3 (32-36). Control was obtained in 94% of the patients treated shortly after surgery but only in 70% of patients who were treated after clinical recurrence. From these data one can conclude that immediate radiotherapy improves the chance of cure after incomplete surgery. However, there were no significant differences in survival between the irradiated and nonirradiated pathologic stage C patients. Therefore, the Southwestern Oncology Group is conducting a prospective randomized study comparing observation versus postoperative radiation therapy for pathologic stage C prostate cancer.

Assessment of Local Control: Significance of Post Radiotherapy Biopsy

In the majority of cases, cancer of the prostate is a slowly growing tumor but simultaneously is a slowly regressing tumor. Until there is better systemic management of prostate cancer, local control is the only realistic goal of local therapy, whether radiation treatment or surgery.

Avoiding the distressing symptoms which result from local failure contributes to quality of life and is an important goal of

Table 3
**Postprostatectomy Radiation Therapy
After Local Recurrence**

Series	Number of Locally Controlled/ Number of Patients	Five-Year Survival (%)
Rosen et al (32)	10/13	15
Gibbons et al (33)	16/23	40
Hanks & Dawson (34)	8/10	71
Ray et al (35)	11/19	40
Total	45/65 (70%)	

radiation therapy (37). Assessment of local results immediately after radiotherapy may be misleading because it may require many months after treatment to achieve complete regression. Perez et al (38,39) found complete regression three months after radiotherapy in 44% of stage B and 22% of stage C patients, whereas the ultimate local control rates were 89% and 66%, respectively.

Cox and Kline (40) performed serial biopsies of the prostate in patients with stage C disease after external beam radiation therapy. The number of positive biopsies fell from 66% three to six months after therapy to 19% two to three years later. They found that after adequate irradiation, positive biopsies performed even one to two years later did not predict the ultimate result. In contrast to this series, a study of prostate biopsies 6 to 36 months after completion of radiotherapy does show a correlation between positive posttreatment biopsy and progressive disease (41). If any biopsy was positive, 60% of the patients eventually developed local recurrence; with negative biopsies, only 19% developed local recurrence. This issue will not be resolved until a prospective trial is conducted. However, periodic digital examination is considered adequate to evaluate local control, and biopsy can be limited to those patients who have clinical evidence of progression.

Prostate-Specific Antigen as a New Tumor Marker

Prostate-specific antigen (PSA) is a useful tumor marker for monitoring response to radiotherapy in patients with prostate cancer. The test can identify patients at risk for failure, allowing early intervention with hormone therapy or chemotherapy. PSA is far superior to acid phosphatase in predicting treatment failure. The decline in serum levels of PSA after "definitive" radiation for localized prostate cancer is much delayed when compared to the drop after surgical excision, but it is nonetheless useful prognostically. In the Stanford series serial values were stable after one year in 49% of the patients but were increasing in 51% (42,43). Relapse should be suspected if the PSA is not normal within six months after completion of radiation therapy.

Future studies may further define the role of PSA as an indication of early relapse of prostate cancer.

Summary and Future Prospects

The efficacy of radiation therapy in the treatment of early stages of prostate cancer has been well established. In cancers limited to the prostate gland, results of radiotherapy are as good as that of radical prostatectomy. Because of the comparable long-term tumor control rates, patients with early stages of prostate cancer have various options for curative treatment. These include radical prostatectomy, radionuclide brachytherapy, and external beam radiation therapy. Stage of the tumor, histologic grade, size of the primary tumor, and overall medical conditions of the patient must all be considered in selecting a therapeutic modality.

Considerable progress has been made in delivering high tumoricidal doses of radiation using external beam therapy. Highly focused precision delivery of radiation is feasible be-

cause of improved imaging techniques and complex multiple field arrangements. There has also been significant technical progress in the use of brachytherapy. Radioiodine-125 can be implanted successfully in most patients with early stage, low-grade prostate cancers utilizing a CT-guided transperineal approach.

For locally advanced stages of prostate cancer, a variety of new technological and radiobiological approaches are being evaluated at our institution. These include the use of a multileaf collimated linear accelerator to deliver three-dimensional external beam radiotherapy. Evaluation of concomitant chemotherapy and radiotherapy is well under way for patients with localized prostatic cancer of high-grade histology. Other experimental modalities such as hyperthermia, photodynamic therapy, and radiation chemical sensitizers may prove to be of value.

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