

The Radial Distance of Extraprostatic Extension of Prostate Carcinoma

Implications for Prostate Brachytherapy

Brian J. Davis, M.D., Ph.D.¹
 Thomas M. Pisansky, M.D.¹
 Torrence M. Wilson, M.D.²
 Harold J. Rothenberg, M.D.³
 Anna Pacelli, M.D.³
 David W. Hillman, M.S.⁴
 Daniel J. Sargent, Ph.D.⁴
 David G. Bostwick, M.D.^{2,3}

¹ Division of Radiation Oncology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

² Department of Urology and Laboratory Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

³ Department of Pathology and Laboratory Medicine; Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

⁴ Cancer Center Statistics Unit, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Presented at the American Society of Therapeutic Radiology and Oncology Meeting, Phoenix, Arizona, October 25–29, 1998.

Address for reprints: Brian J. Davis, M.D., Ph.D., Division of Radiation Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

Received February 25, 1999; accepted March 5, 1999.

BACKGROUND. Extraprostatic extension (EPE) is an unfavorable prognostic factor in patients with prostate carcinoma. Prior studies have reported the linear extent of EPE measured circumferentially along the edge of the prostate. In this study, the authors defined and evaluated a novel measure of EPE in a large series of radical prostatectomy specimens. These results have important clinical implications in the management of localized prostate carcinoma by brachytherapy and other modalities.

METHODS. The authors reviewed the preoperative records and biopsy findings from 376 patients who underwent radical retropubic prostatectomy between September 1991 and June 1993. Whole mount radical prostatectomy specimens were examined, and the location of EPE for each specimen was recorded. The radial EPE distance was measured perpendicular to the edge of the prostate. For specimens with multiple EPE sites, the maximum radial EPE distance was recorded. Established eligibility criteria for prostate brachytherapy were evaluated using these results, with emphasis placed on achieving adequate radiation dose coverage 3–5 mm beyond the capsule or the edge of the prostate.

RESULTS. EPE was identified in 105 of 376 specimens (28%) at 248 sites. The radial EPE distance in these specimens had a mean of 0.8 mm (range, 0.04–4.4 mm) and a median of 0.5 mm. Of these 105 patients, the median and mean preoperative prostate specific antigen (PSA) concentrations were 11.8 ng/mL and 17.9 ng/mL, respectively. The mean and range of the Gleason score and prostate volume for all specimens were 6.3 (range, 3–9) and 39 cc (range, 8–294 cc), respectively. In 107 patients who met the selection criteria for prostate brachytherapy eligibility of a PSA level < 10 ng/mL, Gleason score < 7, and gland volume < 60 cc, the maximum and mean radial EPE distances were 0.6 mm and 0.03 mm, respectively.

CONCLUSIONS. The radial distance of EPE is an important measure that influences treatment strategies for patients with localized prostate carcinoma. Currently described criteria for the treatment of early stage prostate carcinoma by brachytherapy alone appear satisfactory to ensure effective radiation dose coverage of EPE of prostate tumors. Treating the prostate with a 3–5 mm margin by brachytherapy would encompass all known tumor in approximately 99% of the specimens examined in this study. *Cancer* 1999;85:2630–7.

© 1999 American Cancer Society.

KEYWORDS: brachytherapy, extraprostatic extension, pathology, prostatectomy, prostatic neoplasms/pathology, prostatic neoplasms/surgery, radiotherapy.

In 1998, it is estimated that 184,500 men in the United States will be diagnosed with adenocarcinoma of the prostate, and 39,200 men will die from this carcinoma.¹ Early detection efforts, including the use of serum prostate specific antigen (PSA) concentration, identify

patients with organ-confined prostate carcinoma.² External beam radiation therapy (EBRT) and radical prostatectomy are two common treatment options for low stage prostate carcinoma.³ In many medical centers, the presence of clinically evident extraprostatic extension (EPE) is a contraindication to surgery. In such cases, patients often receive EBRT, which allows for treatment of a wider margin of periprostatic tissues. Recently, prostate brachytherapy with temporary or permanent placement of radionuclides has reemerged as an alternative method of treatment for patients with clinically localized prostate carcinoma. This resurgence has stemmed from technical advances in the use of transrectal ultrasound (TRUS) for needle guidance with perineal templates^{4,5} and computed tomography (CT) and TRUS-based dosimetry with sophisticated treatment planning software.

Prostate brachytherapy has several advantages, including its application to an outpatient setting, minimal invasiveness, rapid patient recovery period, and cost effectiveness. Although the published follow-up of patients treated with prostate brachytherapy is shorter than for other treatment modalities, relapse free survival rates appear comparable to EBRT or radical prostatectomy at 7 years.^{6,7} The presence of EPE is important in determining acceptable treatment for localized adenocarcinoma of the prostate. We hypothesized that the technical approach to its treatment also depends on the radial extent of EPE perpendicular to the prostatic capsule, a concept that, to our knowledge, has not been studied previously. For EBRT, the treatment volume typically extends 1 cm or more beyond the edge of the prostate, as identified by CT.⁸⁻¹⁰ For brachytherapy, the goal is to encompass the entire prostate with a dose considered adequate for eradication of all cancer. This dose for a permanent iodine-125 (I-125) implant is typically 14,500–16,000 centigrays (cGy) at the periphery of the target volume, which typically extends 3–5 mm beyond the edge of the prostate.⁷ At the periphery of a prostate implanted with radioactive seeds, the dose gradient can be >2000 cGy/mm in the region of the dose fall-off.¹¹ This steep dose gradient results from the sum of the dose profiles of each radioactive seed, which, individually, have a dose profile obeying the inverse square law, $D \propto 1/r^2$, where the dose, D , is proportional to $1/r^2$, and r^2 represents the square of distance from the source.¹² It is the location of this dose gradient relative to the prostate periphery in the presence of EPE and adjacent normal structures that deserves critical attention.

Failure to cover the entire prostate with a sufficient dose results in local tumor recurrence,^{13,14} which probably is associated with a poorer distant metastasis

free survival.¹⁵ Significant differences in local relapse free survival were found for delivered doses <14,000 cGy in the Memorial Sloan-Kettering experience with retropubic implants^{13,14} and for the transperineal approach, as reported recently by Stock et al.¹⁶ When treatment margins are too generous, rectal ulceration and fistulae may result from radiation injury.¹⁷ Therefore, close examination of the location and magnitude of the radial distance of EPE of tumor may allow an objective means by which to plan for adequate coverage of the cancer and minimize radiation exposure of adjacent normal tissues.

The predictive accuracy for determining the presence of EPE by digital rectal examination or by radiographic means is low.¹⁸⁻²² In one series of 311 serially sectioned radical prostatectomies removed for localized carcinoma, clinical understaging and overstaging were observed in 59% and 5% of cases, respectively.²³ Other series have confirmed this tendency toward clinical understaging, with rates ranging from 43% to 63%.¹⁸⁻²² The presence of EPE has been shown to be associated with serum PSA concentration, clinical stage (as determined by digital examination), grade, and percent of specimen involved with tumor.^{23,24} Another model^{25,26} adapted from the prostatectomy data of Partin et al.²² used preoperative PSA and Gleason score to predict EPE. However, these predictive models did not examine the radial distance of EPE.

Some patients with clinically organ-confined disease are not considered suitable candidates for prostate brachytherapy by current practice parameters due to adverse prognostic factors that predict a high likelihood of clinically occult extraprostatic carcinoma.²⁷ These patients may be treated by combination brachytherapy and EBRT²⁷ or by EBRT alone. The rationale for this approach is clear: The greater the likelihood of clinically occult yet significant extraprostatic carcinoma, the smaller the probability that adequate radiation will be delivered to the extraprostatic disease from an intraprostatic permanent interstitial implant. Although some^{5,27-29} have proposed selection criteria for patients receiving treatment with prostate brachytherapy alone (monotherapy), these criteria are related to the probability of EPE but not to its radial distance. In this context, we evaluated the radial extent of EPE to relate these findings to typical prostate brachytherapy dosimetry. This effort was conducted to facilitate further development of treatment selection criteria for prostate brachytherapy and to provide useful data for EBRT and surgical management of early stage prostate carcinoma.

MATERIALS AND METHODS

Patients

Between September 1991 and June 1993, a total of 416 consecutive radical retropubic prostatectomy specimens from three urologic surgeons were submitted for total embedding and wholemounting. Forty patients with prior androgen ablation, radiotherapy, or clinical T3 disease were excluded, leaving a total of 376 patients for evaluation. Clinical staging of tumors was based on the 1997 American Joint Committee on Cancer (AJCC) system;³⁰ T1 was defined as tumor that clinically was not apparent by digital examination or imaging, and T2 was defined as tumor clinically confined to the prostate. Preoperative serum PSA concentrations were determined by using the Hybritech Tandem R PSA assay (Hybritech, Inc., San Diego, CA) through August 30, 1992. Thereafter, the Abbott IMX automated assay (Abbott Laboratories, Abbott Park, IL) was used.

Method of Wholemounting

The Mayo Clinic routine partial sampling protocol for preparing and reporting serially sectioned wholemount prostates has been described previously.³¹ Biopsy and radical prostatectomy specimens were graded histologically according to the Gleason system. The wholemount sections were examined, and "maps" of tumor size, shape, and location were made by tracing the outlines of the prostate and the mass(es) within it on each slide simply by placing the glass slide and the recording form on 8.5×11 inch paper on a lighted X-ray viewing box. Each slide was marked with ink to show the three possible conditions of tumor spread relative to the capsule: 1) no involvement of capsule, 2) extension into the capsule but not through it, and 3) extension through the full thickness of the capsule and into the extraprostatic tissue. Patients in the third group form the primary focus of this study.

Measurement of the Radial Distance of EPE

Radial extension is the measurement taken for EPE. An example of EPE is shown in the photomicrograph in Figure 1. The corresponding EPE measurement shown in schematic representation also is presented in Figure 1. Radial EPE distance is defined as the distance that the tumor protrudes perpendicularly beyond the outer margin of the capsule. If the collagen fibers of the usual prostate capsule were not visible, then the interface between microscopically recognizable prostate tissue and fat cells or a desmoplastic reaction of inflammatory cells and fibroblasts were considered to be the equivalent of the capsule. When-

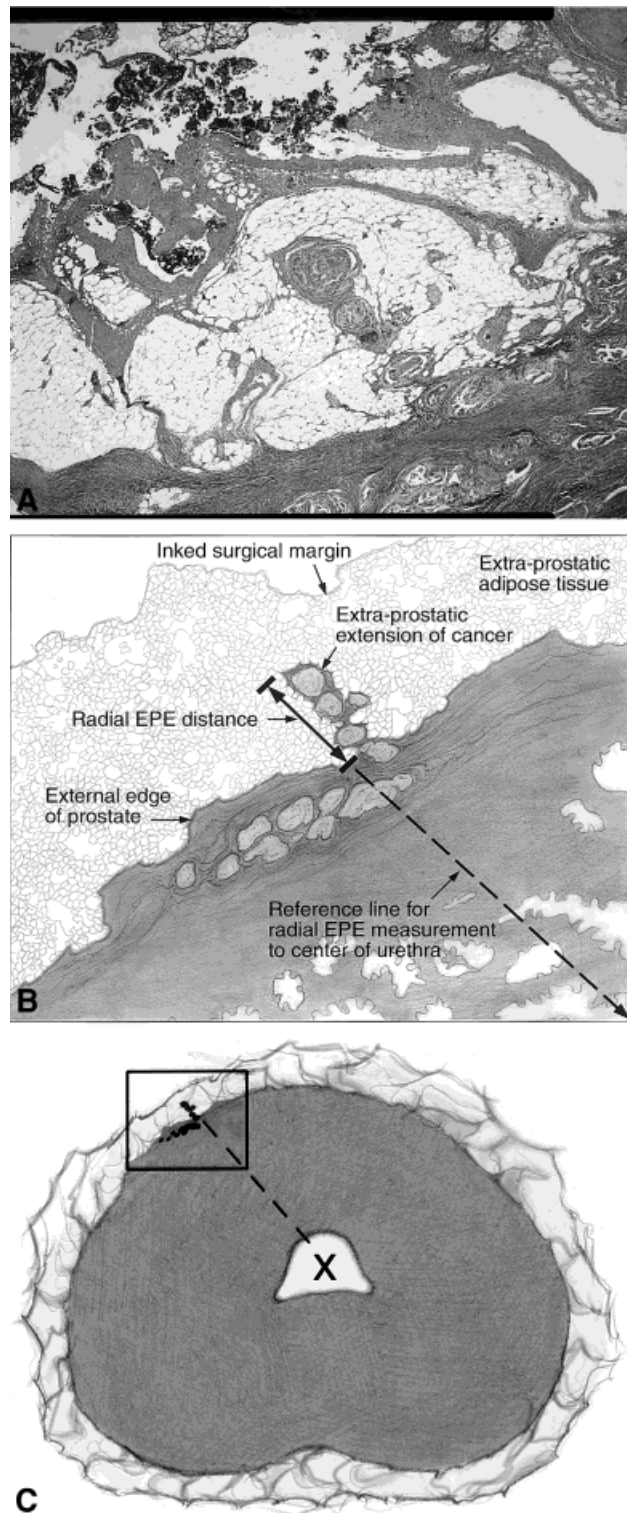


FIGURE 1. (A) Photomicrograph of extraprostatic extension (EPE) of adenocarcinoma. (B) Schematic representation of the radial EPE distance from A. Note that this distance is measured perpendicularly to the capsule and is centered on the urethra. (C) Schematic representation of the prostate from which the radial EPE distance was measured with inset shown.

ever possible, the urethra was used as the anatomic center in each section along which the radial EPE distance direction was measured (see Fig. 1). Observations and measurements were made by using a Zeiss Axioskop microscope (Zeiss, Inc., Thornwood, NY). A commercially manufactured stage micrometer (2.00 mm ruled in 0.01 mm increments) (American Optical Co.) was used to calibrate the corresponding 100-unit ocular reticle. Calibrations were performed before each series of measurements.

In contrast to studies in which volume is calculated and a shrinkage factor associated with tissue processing is employed,²³ no linear shrinkage factor was used in this study. The overall net linear shrinkage factor is between 4.3%³² and 7.7%²³ (volume correction factor^{1/3} = linear correction factor, $1.25^{1/3} = 1.077$), which is small and not considered significant for the purposes of this study.

The location of all EPE sites was recorded for all specimens with respect to the craniocaudad (bladder base, superior, middle, or inferior), lateral (right or left), and anterior-posterior (anterior, lateral, or posterior) directions. Measurement of radial EPE distance in specimens with multiple sites of EPE was recorded for the site of maximum extension. For example, if there were four sites of EPE in a specimen, then the value recorded was that for the site with the maximum radial distance but not for the radial EPE distances for the other three sites. If there was a positive margin at the site of EPE but this was the maximal distance, then the distance from the capsule or periphery of the prostate to the positive margin at the EPE site was recorded.

RESULTS

The mean and range of Gleason score and prostate volume were 6.3 (range, 3–9) and 39 (range, 8–294 cc), respectively, for all specimens. Preoperative serum PSA levels ranged from 0.3 ng/mL to 98 ng/mL, with median and mean values of 8.6 ng/mL and 12.4 ng/mL, respectively. Information regarding patient age, date of operation, Gleason score, and nuclear grade is shown in Table 1.

A total of 248 EPE sites were identified in 105 prostatectomies. The mean, median, and range of radial distance of EPE for those specimens with EPE were 0.8 mm, 0.5 mm, and 0.04–4.4 mm, respectively. The distribution of the radial EPE distance is shown in Figure 2. The cumulative percentage of cases with a radial distance of EPE less than a given distance also is shown in Figure 2. For example, 96% of all specimens with EPE have a radial EPE distance \leq 2.5 mm. In 27 specimens, the site of maximal EPE distance was measured at a site of positive margin (Table 2).

TABLE 1
Relation between Disease Related Characteristics and Extraprostatic Extension in 376 Patients

Preoperative variable and specimen characteristic	No. of patients	Extraprostatic extension (%)		
		None	0.01–3.00 mm	>3.0 mm
Age at operation (yrs)				
< 60	85	71	29	0
60–69	196	73	26	1
\geq 70	95	71	29	0
PSA (ng/mL)				
< 4	61	88	12	0
4.0–9.9	158	78	22	0
10.0–19.9	105	68	30	2
\geq 20.0	52	44	56	0
Clinical T stage				
T1a–T2a	163	86	13	1
T2b	213	61	39	0
Gleason score				
3–4	16	100	0	0
5–6	134	84	16	0
7–9	226	63	36	1
Nuclear grade				
1	14	100	0	0
2	348	72	27	1
3	14	36	64	0
Prostate volume (cc)				
< 30	168	70	30	0
30–39	97	74	25	1
\geq 40	111	73	26	1
Date of surgery				
9/91–3/92	136	71	28	1
4/92–9/92	110	67	33	0
10/92–6/93	130	77	22	1

PSA: prostate specific antigen.

Among the patients with EPE, sites of EPE were distributed evenly between left (52%) and right (48%) sides of the prostate. The majority of sites were in the midprostate (57%) compared with inferior (5%) or superior (38%) locations. The anterior prostate had 15% of sites compared with the lateral (28%) and posterior (56%) locations. The bladder base had <1% of all sites of EPE. For specimens with EPE, the mean number of sites was 2.4, the median number was 2 sites, and the range was 1–10 sites. Forty-three specimens (41%) showed one site of EPE, 22 specimens (21%) showed 2 sites, 19 specimens (18%) showed 3 sites, 9 specimens (9%) showed 4 sites, and 12 specimens (11%) showed 5–10 sites.

The observed rate and radial distance of EPE also were evaluated with respect to pretherapy serum PSA, Gleason score, and prostate volume characteristics that may be considered as criteria for the selection of patients for prostate implantation as monotherapy.

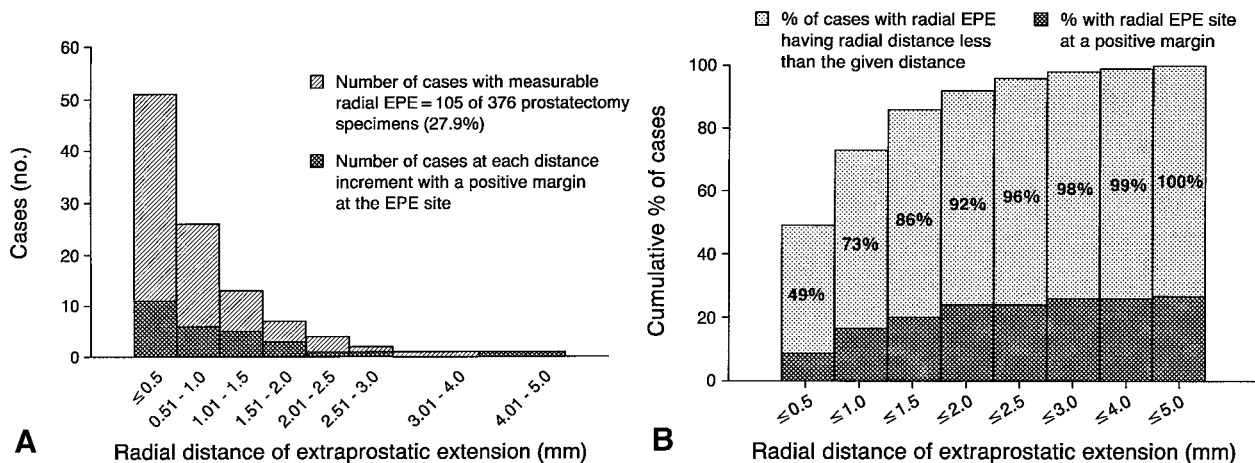


FIGURE 2. (A,B) Distribution and cumulative percentage of radial extraprostatic extension (EPE) distance (mm) with information regarding margin status at measurement sites.

TABLE 2
Distribution of Radial Distance of Extraprostatic Extension

Distance (mm)	No. (%)	Cumulative % of cases	Number (%) positive margins at EPE site
≤ 0.5	51 (49)	49	11 (22)
0.51-1.0	26 (25)	73	6 (23)
1.01-1.5	13 (12)	86	5 (38)
1.51-2.0	7 (7)	92	3 (43)
2.01-2.5	4 (4)	96	0 (0)
2.51-3.0	2 (2)	98	1 (50)
3.01-4.0	1 (1)	99	0 (0)
4.01-5.0	1 (1)	100	1 (100)

EPE: extraprostatic extension.

These patient categories are shown in Table 3, along with the entire study population and the cohort with EPE for comparison purposes. For patients with EPE, the median and mean preoperative PSA were 11.8 ng/mL and 17.9 ng/mL, respectively. In the 219 patients (58% of the total) with PSA < 10 ng/mL, the maximum radial distance of EPE was 2.1 mm. In the 150 patients (40% of the total) with Gleason score < 7, the maximum radial distance of EPE was 2.16 mm. In the 107 patients (28% of the total) who met the selection criteria for prostate brachytherapy eligibility of PSA < 10 ng/mL, Gleason score < 7, and gland volume < 60 cc, the maximum and mean radial EPE distances were 0.6 mm and 0.03 mm, respectively. Only 11 such patients (10%) had EPE.

DISCUSSION

We measured the radial distance of EPE present in 376 wholemount radical prostatectomy specimens. Accu-

rate preimplantation knowledge of anatomic extent of disease is clinically useful for brachytherapy planning. Brachytherapy preplanning includes determining radioisotope type, number, activity (in milliCuries), and desired seed location within and around the prostate. Selection of an appropriate treatment margin around the prostate is instrumental in defining properly the planning target volume that is to receive the minimum prescribed radiation dose. A quantitative pathologic assessment of subclinical tumor invasion from the primary tumor into adjacent structures or regional lymphatic tissues forms the basis for EBRT or brachytherapy planning. Examples of this concept have been applied successfully for other cancer sites, including EBRT for melanoma,^{33,34} high grade gliomas,^{35,36} and early stage breast carcinoma.³⁷ The observations presented in this report may have similar clinical relevance in the context of prostate carcinoma management.

The presence of positive margins in these data is an expected feature of a prostatectomy series. In some cases (26%), the EPE sites where the radial distance was measured included tumor positive surgical margins. The location of the positive margins with respect to the measured radial distances is included in Figure 2. The true radial EPE distance may be underestimated at sites of positive margins. It is unlikely, however, that the radial EPE distance is underestimated substantially for tumors that are clinically organ confined, because significant EPE may be appreciated by DRE or by radiographic means, such as CT, magnetic resonance imaging, or TRUS.

A potential limitation of this study is the inherent selection bias associated with using pathologic data from prostatectomy specimens and applying it to

TABLE 3
Influence of Common Treatment Selection Criteria on the Radial Distance of Extraprostatic Extension and Patient Number

Patient group	Number of patients	Number of patients with EPE > 0 mm	Range of EPE _r (mm)	Mean EPE _r (mm)	Median EPE _r (mm)	Positive margins at EPE site (%)
All Patients	376	105	0-4.4	0.22	0	9
Patients with EPE	105	105	0.04-4.4	0.81	0.5	26
Patients with PSA < 10 ng/mL	219	42	0-2.1	0.13	0	3
Patients with Gleason score < 7	150	21	0-2.16	0.06	0	1
Patients with PSA < 10, Gleason score < 7, and prostate volume < 60 cc	107	11	0-0.6	0.03	0	0

EPE: extraprostatic extension; EPE_r: radial distance of EPE; PSA: prostate specific antigen.

prostate brachytherapy. The widespread use of serum PSA identifies patients with clinically impalpable prostate carcinoma.² Since the time these specimens were obtained (1991-1993), there has been a progressive decrease in the proportion of patients who present for prostatectomy with palpable tumors, as reported recently by Amling et al.² The selection bias favoring palpable tumors in our data may serve to overestimate the proportion of patients with clinically significant EPE who are ineligible for prostate brachytherapy. To confirm our data, additional specimens collected in a prospective manner from patients who are found suitable for prostate brachytherapy but who elect to undergo prostatectomy would be desirable.

Previous studies have quantified EPE in terms of the area of capsular perforation³⁸ or the linear extension along or parallel to the capsule.³⁹ These approaches do not provide the critical measurement applicable to prostate brachytherapy that is provided by the radial EPE distance measurement. The steepest radiation dose gradient for prostate brachytherapy is in the direction away from the center of the implanted gland and not in a direction circumferential or tangential to it.¹¹ Clearly, the radial distance perpendicular to the capsule is the limiting factor in treatment of extraprostatic carcinoma with intraprostatic radioactive sources.

The information presented in Table 3 suggests a possible correlation between preoperative serum PSA level, Gleason score, and radial distance of EPE. As criteria become more restrictive with respect to patient eligibility, the maximum radial distance of EPE and the percent of patients with EPE decreases. To verify this correlation, we contemplated developing models to predict the radial distance of EPE as a function of preoperative and specimen variables. Standard statistical modeling approaches using our data require clinically meaningful breakpoints for radial EPE distance, such as 3 mm or 5 mm. However,

only two patients (less than 1% of the total series) showed a radial distance of EPE >3 mm, which is an insufficient number of patients to provide adequate statistical power for such an analysis.

The site of EPE is important in planning prostate brachytherapy and for other forms of local therapy for early stage disease. In this study, the midposterior prostate was the most likely location for EPE. Fully one-third of EPE sites were at this location, suggesting that significant attention should be paid to the accurate placement of radioactive seeds in this region. Placement of seeds too close to or into the rectal wall may lead to rectal complications, including ulceration and fistulae caused by a high radiation dose.^{17,29} If EPE is present, then these results suggest that implantation of seeds too far from the midposterior prostatic capsule may lead to radiation underdosage. Implantation of seeds in the periprostatic tissues particularly near the prostatic apex and base is a common practice.⁵ This practice allows radiation to be delivered to extraprostatic sites but, in some instances, may be limited because a small portion of seeds may migrate through the venous circulation and become lodged in pulmonary capillaries.^{40,41} The data presented here indicate that few sites of EPE are found near the bladder base or prostatic apex. Routine implantation of seeds in these extraprostatic locations might not be necessary so long as the entire prostate itself is adequately treated.

Commonly used criteria for prostate brachytherapy alone without adjuvant external beam radiotherapy include PSA < 10 ng/mL, Gleason score < 7, prostate volume < 60 cc, peak urine flow rate on urodynamic study > 10 cc/second, and American Urological Association Obstructive Symptom Index < 16.^{5,7,29} The often stated purpose of these criteria is to select for patients with a low probability of extraprostatic disease (including seminal vesicle invasion, lymph node metastases, and distant metastases), pu-

bic arch interference, and postimplant obstructive symptoms. Patients with Gleason score < 7, PSA < 10, and prostate volume < 60 cc had maximum and mean radial EPE distances of 0.6 mm and 0.03 mm, respectively. By using these criteria, all patients had a radial EPE distance < 3 mm and would therefore have received adequate radiation dose coverage had these patients undergone brachytherapy. In addition, no patients who met these criteria had EPE measured at a positive margin site, thus eliminating a potential source of uncertainty.

The selection of PSA concentration and Gleason score criteria that make patients eligible for monotherapy should be correlated with a patient's risk of seminal vesicle invasion,⁴² lymph node involvement,⁴³ or bone metastases.⁴⁴ The appropriate and tolerable risk levels for these parameters should dominate the decision making process for patient eligibility. Clinically occult EPE is likely to be treated adequately by a prostate seed implant when suitable radiation dose margins are achieved. Examining wholemount prostatectomy specimens for the radial distance of EPE is useful for evaluating prostate brachytherapy technique and selection criteria. Positive surgical margins are a significant predictor of recurrence in Stage pT2N0 disease⁴⁵ and may be unavoidable with the limits of resection allowed by current techniques and the radial distance of EPE. Similar to the approach taken in this study, measurement of the radial distance of resection margins and positive margins likewise may be beneficial.

In conclusion, we present data on the radial distance of EPE perpendicular to the edge of the prostate that, to our knowledge, have not been reported previously. These data are useful for evaluating treatment strategies for successful prostate brachytherapy and other modalities in the treatment of localized prostate carcinoma. With respect to prostate brachytherapy by permanent transperineal interstitial implantation of radioactive sources, currently described criteria for treatment of early stage prostate carcinoma by brachytherapy alone appear satisfactory to allow radiation dose coverage of EPE of cancer and may be unnecessarily restrictive. Nevertheless, treatment of the prostate with a 3–5 mm margin by brachytherapy would encompass all known disease in 99–100% of the specimens with EPE and in 99.5–100% of all specimens that were examined in this study.

REFERENCES

- Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. *CA Cancer J Clin* 1998;48:6--29.
- Amling CL, Blute ML, Lerner SE, Bergstralh EF, Bostwick DG, Zincke H. Influence of prostate-specific antigen testing on the spectrum of patient with prostate cancer undergoing radical prostatectomy at a large referral practice. *Mayo Clin Proc* 1998;73(5):401–6.
- Millikan R, Logothetis C. Update of the NCCN guidelines for treatment of prostate cancer. *Oncology* 1997;11(11A):180.
- Holm HH, Juul N, Pedersen JF, Hansen H, Stroyer I. Transperineal iodine-125 seed implantation in prostate cancer guided by transrectal ultrasonography. *J Urol* 1983;130:283–6.
- Blasko JC, Wallner K, Grimm PD, Ragde H. Prostate specific antigen based disease control following ultrasound guided 125 iodine implantation for stage T1/T2 prostatic carcinoma. *J Urol* 1995;154(3):1096–9.
- Pollack A, Zagars GK. External beam radiotherapy for stage T1/T2 prostate cancer: how does it stack up? *Urology* 1998;51:258–64.
- Ragde H, Blasko JC, Grimm PD, Kenny GM, Sylvester JE, Hoak DC, et al. Interstitial iodine-125 radiation without adjuvant therapy in the treatment of clinically localized prostate carcinoma. *Cancer* 1997;80:442–53.
- Leibel SA, Heimann R, Kutcher GJ, Zelefsky MJ, Burman CM, Melian E, et al. Three-dimensional conformal radiation therapy in locally advanced carcinoma of the prostate: preliminary results of a Phase I dose-escalation study. *Int J Radiat Oncol Biol Phys* 1994;28:55–65.
- Hanks GE, Hanlon AL, Schultheiss TE, Freedman GM, Hunt M, Pinover WH. Conformal external beam treatment of prostate cancer. *Urology* 1997;50(1):87–92.
- Pickett B, Roach M, Verhey L, Horine P, Malfatti C, Adazawa C, et al. The value of nonuniform margins for six-field conformal irradiation of localized prostate cancer. *Int J Radiat Oncology Biol Phys* 1995;32(1):211–8.
- Dawson JE, Wu T, Roy T, Gu JY, Kim H. Dose effects of seed placement deviations from pre-planned positions in ultrasound guided prostate implants. *Radiother Oncol* 1994;32(3):268–70.
- Nath R, Anderson LL, Luxton G, Weaver KA, Williamson JF, Meigooni AS. Dosimetry of interstitial brachytherapy sources: recommendations of the AAPM Radiation Therapy Committee Task Group no. 43. *Med Phys* 1995;22(2):209–34.
- Fuks Z, Leibel SA, Wallner KE, Begg CB, Fair WR, Anderson LL, et al. The effect of local control on metastatic dissemination in carcinoma of the prostate: long-term results in patients treated with 125I implantation. *Int J Radiat Oncol Biol Phys* 1991;21(3):537–47.
- Zelefsky MJ, Whitmore WF. Long-term results of retropubic permanent 125 iodine implantation of the prostate for clinically localized prostatic cancer. *J Urol* 1997;158:23–30.
- Yorke ED, Fuks Z, Norton L, Whitmore W, Ling CC. Modeling the development of metastases from primary and locally recurrent tumors: comparison with a clinical data base for prostatic cancer. *Cancer Res* 1993;53(13):2987–93.
- Stock RG, Stone NN, Tabert A, Iannuzzi C, DeWyngaert JK. A dose-response study for I-125 prostate implants. *Int J Radiat Oncol Biol Phys* 1998;41:101–8.
- Stromberg J, Martinez A, Benson R, Garton G, Diokno A, Gonzalez J, et al. Improved local control and survival for surgically staged patients with locally advanced prostate cancer treated with up-front low dose rate iridium-192 prostate implantation and external beam irradiation. *Int J Radiat Oncol Biol Phys* 1994;28:67–5.
- Catalona WJ, Bigg SW. Nerve-sparing radical prostatectomy: evaluation of results after 250 patients. 1990;143:538.

19. Paulson DF, Moul JW, Walther PJ. Radical prostatectomy for clinical stage T1-2NOMO prostatic adenocarcinoma: long-term results. *J Urol* 1990;144:1180.
20. Stein A, DeKernion JB, Smith RB, Dorey F, Patel H. Prostate specific antigen levels after radical prostatectomy in patients with organ confined and locally extensive prostate cancer. *J Urol* 1992;147:942.
21. Rosen MA, Goldstone L, Lapin S, Wheeler T, Scardino PT. Frequency and location of extracapsular extension and positive surgical margins in radical prostatectomy specimens. *J Urol* 1992;148:331.
22. Partin AW, Pound CR, Clemens JQ, Epstein JI, Walsh PC. Serum PSA after anatomic radical prostatectomy. The Johns Hopkins experience after 10 years. *Urol Clin North Am* 1993;20(4):713.
23. Bostwick DG, Qian J, Bergstralh E, Dundore P, Dugan J, Myers RP. Prediction of capsular perforation and seminal vesicle invasion in prostate cancer. *J Urol* 1996;155:1361.
24. Kleer E, Oesterling JE. PSA and staging of localized prostate cancer. *Urol Clin North Am* 1993;20(4):695-704.
25. Chen, A, Roach M, Diaz A, Marquez C, Chinn D, Coleman L, et al. Using Pre-treatment PSA and Gleason score to predict for extra capsular extension among patients with clinically staged organ confined prostate cancer [abstract 1020]. *Int J Radiat Oncol Biol Phys* 1995;32:232.
26. Roach M. Equations for predicting the pathologic stage of men with localized prostate cancer using the preoperative prostate specific antigen (PSA) and Gleason score. *J Urol* 1993;150:1923.
27. Dattoli M, Wallner K, Sorace R, Koval J, Cash J, Acosta R, et al. 103Pd brachytherapy and external beam irradiation for clinically localized, high-risk prostatic carcinoma. *Int J Radiat Oncol Biol Phys* 1996;35:875-9.
28. Stock RG, Stone NN, DeWyngaert JK, Lavagnini P, Unger PD. Prostate specific antigen findings and biopsy results following interactive ultrasound guided transperineal brachytherapy for early stage prostate carcinoma. *Cancer* 1996;77:2386-92.
29. Wallner K, Roy J, Harrison L. Tumor control and morbidity following transperineal iodine 125 implantation for stage T1/T2 prostatic carcinoma. *J Clin Oncol* 1996;14:449-53.
30. American Joint Committee on Cancer. Manual for staging of cancer. Philadelphia: Lipincott, 1997.
31. Bostwick DG, Myers RP, Oesterling JE. Staging of prostate cancer. *Semin Surg Oncol* 1994;10:60-72.
32. Schned AR, Wheeler KJ, Hodorowski CA, Heaney JA, Ernstoff MS, Amdur RJ, et al. Tissue-shrinkage correction factor in the calculation of prostate cancer volume. *Am J Surg Pathol* 1996;20(12):1501-06.
33. Breslow A, Macht SD. Optimal size of resection margin for thin cutaneous melanoma. *Surg Gynecol Obstet* 1977;145:691.
34. Harwood AR. Conventional fractionated radiotherapy for 51 patients with lentigo maligna and lentigo maligna melanoma. *Int J Radiat Oncol Biol Phys* 1983;9:1019.
35. Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. *Neurology* 1980;30:97.
36. Kelly PJ, Dauman-Dupart C, Kispert DB, Kall BA, Scheithauer BW, Illig JJ. Image-based stereotaxic serial biopsies in untreated intracranial glial neoplasms. *J Neurosurg* 1987;66:865.
37. Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas: implication for clinical trials of breast conserving treatment. *Cancer* 1985;56:979.
38. Stamey TA, McNeal JE, Freiha FS, Reedwind E. Morphometric and clinical studies on 68 consecutive radical prostatectomies. *J Urol* 1988;139:1235-41.
39. Epstein JI, Carmichael JM, Pizov G, Walsh PC. Influence of capsular penetration on progression following radical prostatectomy: a study of 196 cases with long-term follow-up. *J Urol* 1993;150:135-41.
40. Wopereis AJM, Moerland JHAG, Battermann JJ. Loss of I-125 seeds after perineal implantation of the prostate. *Radiother Oncol* 1996;40(Suppl 1):S127.
41. Nag S, Scaperroth DD, Badalament R, Hall SA, Burgers J. Transperineal palladium 103 prostate brachytherapy: analysis of morbidity and seed migration. *Urology* 1995;45:87-92.
42. Pisansky TM, Blute ML, Suman VJ, Bostwick DG, Earle JD, Zincke H. Correlation of pretherapy prostate cancer characteristics with seminal vesicle invasion in radical prostatectomy specimens. *Int J Radiat Oncol Biol Phys* 1996;36:585-91.
43. Pisansky TM, Blute ML, Suman VJ, Bostwick DG, Earle JD, Zincke H. Correlation of pretherapy prostate cancer characteristics with histologic findings from pelvic lymphadenectomy specimens. *Int J Radiat Oncol Biol Phys* 1996;34:33-9.
44. Chybowski FM, Keller JJ, Bergstralh EJ, Oesterling JE. Predicting radionuclide bone scan findings in patients with newly diagnosed, untreated prostate cancer: prostate specific antigen is superior to all other clinical parameters. *J Urol* 1992;145:313-8.
45. Blute ML, Bostwick DG, Bergstralh EJ, Slezak JM, Martin SK, Amling CL, et al. Anatomic site-specific positive margins in organ-confined prostate cancer and its impact on outcome after radical prostatectomy. *Urology* 1997;50:733-9.