Brachytherapy Versus Radical Prostatectomy in Patients with Clinically Localized Prostate Cancer

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In an effort to help physicians offer their patients unbiased advice on the best alternatives for treatment of localized prostate cancer, we present a retrospective comparison of the effectiveness of brachytherapy and radical retropubic prostatectomy in 1305 men with stage T1 and T2 adenocarcinoma of the prostate. Data from 1305 patients treated in our community-based private practice urology group from 1993 to 2002 were reviewed, and patients were classified by initial prostate-specific antigen (PSA) level and risk grouping. Risk grouping was defined by preoperative PSA levels and Gleason scores. We used time to PSA-indicated recurrence as the measure of efficacy. Brachytherapy and radical prostatectomy provided similar responses to treatment (no significant differences given the sample size, length of follow-up, and numerical differences observed) for localized prostate cancers. A prospective study is presently underway to evaluate the respective outcome of these procedures (including incidence of incontinence and impotence), and assess their impact on patient quality of life. The results presented here fail to show any superiority of prostatectomy over brachytherapy with palladium-103 (TheraSeed; Theregenics Corp., Buford, GA) with respect to time until relapse indicated by PSA level increase (> 0.2 ng/mL for prostatectomy and >1.5 ng/mL and rising for brachytherapy). In fact, any differences between treatments favor brachytherapy, particularly for intermediate- and high-risk groups. We conclude that both brachytherapy and prostatectomy should be offered, equally and without bias, to men with stage T1 or T2 organ-confined prostate cancer.

Introduction

We believe that early intervention for prostate cancer provides a survival advantage and potential cure. Unfortunately, when a patient with localized prostate cancer seeks information and treatment, he is confronted with the bias of the treating physician and confused by conflicting opinions among different specialists. For example, urologists are more likely to recommend radical prostatectomy, whereas radiation oncologists recommend radiation therapy [1]. Despite less risky treatment options, brachytherapy chief among them, many publications in the urology literature still claim that radical prostatectomy is the "best" way to cure organ-confined cancer, and that brachytherapy need not be considered. No definitive evidence exists for such a claim [2,3].

While a randomized study comparing these two treatment approaches would provide more definitive evidence of their relative efficacy, we believe that such a study is unlikely. Because most clinicians have established preferences, a randomized study would pose ethical problems for them. That being the case, the next best approach is an analysis of outcome data for patients provided with these treatments. Because such non-randomized treatment groups are unlikely to be equivalent with respect to prognostic factors, such an analysis needs to take this inequality into consideration. There are two ways to achieve this: 1) by performing analyses on subsets defined by risk factors; and 2) by performing multivariate analyses that study the effect of treatment while adjusting for other prognostic factors. We report on both approaches below.

Our experience challenges the assumption that prostatectomy has a better cure rate. For the past decade we have been offering—without bias—either radical retropubic prostatectomy or seed implantation to patients with non-palpable lesions discovered by elevated prostate-specific antigen (PSA) (stage T1), or with palpable induration or nodules not reaching the seminal vesicles (stage T2). Because we perform both procedures, we are in an unique position to evaluate and compare the effi-

treatments in our own patients. This report reviews the effects of prostatectomy and brachytherapy in a large population treated in our clinic between 1993 and 2002. The demographics of our patient population indicate 80% of patients in the Medicare age group. For patients over 70 years of age, we often recommend brachytherapy over radical surgery, especially if there are medical comorbidities. This age distribution accounts for the preponderance of patients having implants placed by our group, rather than any lack of surgical experience in performing effective radical prostatectomies with minimal incontinence or other complications.

Methods

Of the 1074 brachytherapy patients and 231 prostatectomy patients treated since January 1, 1993, 869 of the brachytherapy patients and 208 of the prostatectomy patients had data sufficient for inclusion in this report. Details are given in Table 1. These data were collected from patients' charts by our Clinical Research Department and transmitted monthly to an independent statistician for analysis.

Standard staging studies, digital rectal examination, and PSA assays were performed to confirm organ-confined disease, and ultrasonography was used to determine gland size and rule out extracapsular extension. Fourteen to 16 transrectal ultrasound-guided prostate biopsies (including seminal vesicles) were performed, and most patients received bone scans, as well as CT scans of the pelvis. We are a private practice urology group, and each physician counseled his patients on the basis of his experience. The precise techniques used for seed implantation have been described in our previous papers [4,5].

Prostate-specific antigen levels were evaluated 3 months and 6 months after surgery or seed implantation and every 6 months thereafter. In the surgery group, a PSA level greater than 0.2 ng/mL was considered a recurrence; for the brachytherapy group, a PSA level greater than 1.5 and a positive biopsy was considered a recurrence. When biopsies were lacking in patients with PSA levels greater than 1.5 ng/mL, recurrence was declared if this reading was higher than the previous one. In our previous papers we showed statistically that a serum PSA less than 1.5 and not rising was associated with a negative biopsy in more than 95% of patients. Therefore, this level was chosen for defining success or failure. In addition, as time from implant increases, the majority of our patients' PSA levels nadir to 0.5 to 1.0 ng/mL in a statistically significant number (83%–92%, respectively). None of the prostatectomy patients had pre- or postoperative hormone therapy. About half of the patients in the brachytherapy group received Lupron (TAP Pharmaceuticals, Lake Forest, IL) and Eulexin (Schering-Plough, Kenilworth, NJ) 3 months prior to implant and 2 months after. This was done primarily for size reduction of the gland to less than 50 cm^3, and for patients in very high-risk groups, depending on the judgement of the primary urologist in each case. No patient studied in this group received external radiation. In the hopes of improving our results, we recently have begun to add external radiation to the regimen for high-risk groups, and patients with bilateral high volume disease.

The two treatment modalities of brachytherapy and prostatectomy were compared with respect to time to recurrence. This was defined as the time from the date of surgery or seed implantation until the date recurrence was determined (as previously defined) or the date the patient was last seen. There were 62 deaths among the brachytherapy patients and none among the prostatectomy patients. Patients who died without having recurred were considered censored at the date last seen. Because all mortalities were attributed to causes unrelated to the patients' prostate cancer, we felt that this was an appropriate approach. The primary analyses comparing the treatment groups with respect to time to recurrence were by log rank tests specific to initial PSA-level groups and initial risk groups as defined below. In addition, we performed Cox proportional hazards regression to explore the simultaneous effects of multiple variables, including treatment. Statistical analyses of outcomes were done using SAS (version 8.2). Proc Lifetest and Proc Phreg were used for analyses of time to recurrence; and Proc Means and Proc Freq were used for descriptive statistics.

Classification by Severity and Risk

Severity was determined by PSA level at time of initial diagnosis and before any treatment was instituted. By this method, patients were divided into four groups: 0.0 ng/mL to 4.0 ng/mL, 4.1 ng/mL to 10.0 ng/mL, 10.1 ng/mL to 20 ng/mL, and greater than 20 ng/mL. Patients were also classified by "risk group" using a standard that factors in both initial serum PSA and Gleason score. The low-risk group was defined by an initial serum PSA less than or equal to 10.0 ng/mL and a Gleason score of less than 7. The intermediate-risk group showed an initial PSA level greater than 10.0 ng/mL or a Gleason score greater than or equal to 7, but not both concurrently. Finally , the high-risk group had an initial PSA level greater than 10.0 ng/mL and a Gleason score greater than or equal to 7. Although clinical stage is an important prognostic indicator of outcome following both radiation and prostatectomy, we chose this severity/risk classification system for this review of our group's practice in the treatment of prostate cancer.

Patients

Our 9-year review of 1305 charts yielded 1077 patients with sufficient data for inclusion in this report. Of the 1077 patients, 869 were treated with brachytherapy and 208 with prostatectomy. Patients who had prostatectomies were somewhat younger and at slightly higher risk than those who received brachytherapy; otherwise,

Table 1. Data on brachytherapy and prostatectomy patients

	Brachytherapy, *n*	Prostatectomy, *n*
Total patients	1117	282
Stage greater than B or unknown	43	51
Insufficient data	205*	23
Available for analysis	869	208

* 30 with seed implants within 1 year of this analysis.

Table 2. Characteristics of patients treated with brachytherapy or prostatectomy

	Brachytherapy patients (*n*=869)	Prostatectomy patients (*n*=208)
Age, *y*		
Mean	72.3	63.6
Range	48–93	28–79
Initial PSA, *ng/mL*		
< 4.0	29.2 (*n*=254)	33.6 (*n*=70)
4.1–10.0	54.9 (*n*=477)	50.0 (*n*=104)
10.1–20.0	12.0 (*n*=105)	12.0 (*n*=25)
> 20	3.9 (*n*=34)	4.3 (*n*=9)
Gleason score, %		
2–6	70.8 (*n*=601)	64.7 (*n*=134)
7–10	29.2 (*n*=248)	35.3 (*n*=73)
Risk group, %		
Low	61.0 (*n*=528)	56.2 (*n*=117)
Intermediate	32.1 (*n*=278)	35.6 (*n*=74)
High	6.8 (*n*=59)	8.2 (*n*=17)
Stage		
A	22.8 (*n*=198)	8.6 (*n*=18)
B	77.2 (*n*=671)	91.4 (*n*=190)

PSA—prostate-specific antigen.

demographic characteristics in the two groups were similar (Table 2). Mean preoperative PSA levels in in the brachytherapy group were 7.2 ng/mL (with a range between 0.0 and 93 ng/mL) and 6.8 ng/mL (with a range between 0.0 and 61 ng/mL) in the prostatectomy group.

Treatment decisions were made over several weekly visits with patients and spouses. Factors contributing to this decision included careful review of patient's age, sexual potency, bladder outlet obstructive symptoms, risk category (determined by initial PSA level and Gleason score), review of CT scan of pelvis, bone scan, and risks and complications of both potential treatments. Younger patients (less than 70 years of age) were counseled that surgery could not be easily undertaken after brachytherapy without significant increase in complications of incontinence and impotence.

All details of both procedures and their risks of recurrence and complications were repeated at each visit, and patient input and choices were encouraged. We emphasized that failures in both groups would be handled with neoadjuvant hormone therapies, and radiation therapy was a possibility in the prostatectomy group. Patient preference after careful education was the deciding factor.

We are currently engaged in a prospective study to evaluate pre-and postoperative patient quality of life, so we may accurately compare these two treatment groups. This will enhance our ability to precisely educate our patients and definitively state our incontinence and impotence results.

Results

Figures 1A to 1C show Kaplan-Meier estimates of recurrence over time by PSA level group. Time to recurrence is further summarized in Table 3. Recurrence was generally equal in the two groups, with no statistically significant differences observed. Patients with unfavorable initial PSA levels and/or Gleason grades had slightly better results with brachytherapy. For both treatment groups follow-up ranged between 1 and 7 years, with a median follow-up time of 3 years (Table 3). In order to explore further the impact of treatment, taking into account possible differences between the treatment groups with respect to prognostic factors, we also performed a multivariate Cox proportional hazards regression. This methodology models the log of the instantaneous hazard as a linear function of a set of independent variables. The variables of

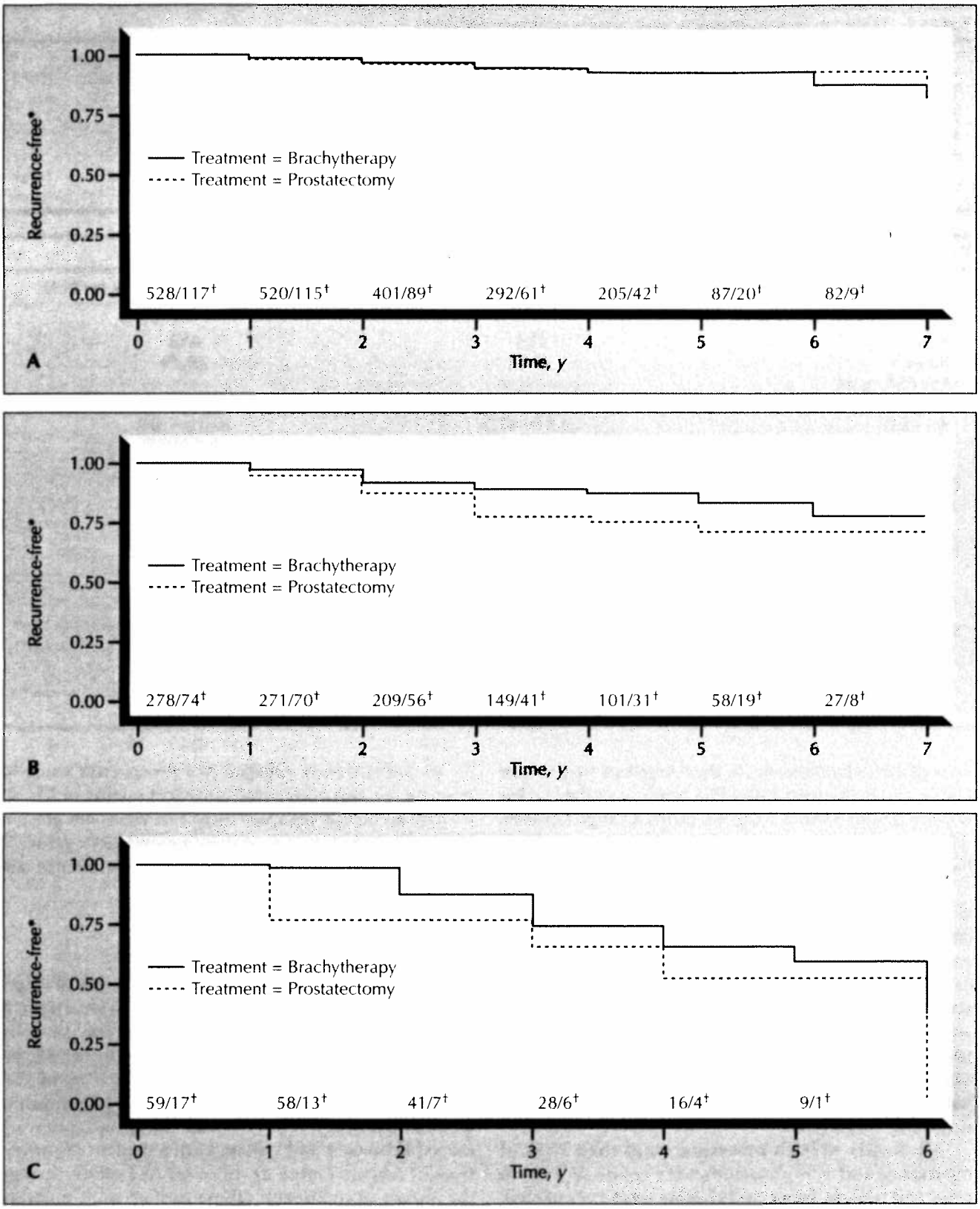

Figure 1. **A**, Kaplan-Meier curves of freedom from prostate-specific antigen (PSA) failure for both treatment groups among patients in the favorable risk group, $P = 0.93$ (log rank test). **B**, Kaplan-Meier curves of freedom from PSA failure for both treatment groups among patients in the intermediate risk group, $P = 0.16$ (log rank test). **C**, Kaplan-Meier curves of freedom from PSA failure for both treatment groups among patients in the unfavorable risk group $P = 0.10$ (log rank test). *Recurrence-free proportions over time in risk group. †Numbers at risk: brachytherapy/prostatectomy.

Table 3. Freedom from recurrence of prostate cancer

	Brachytherapy						Prostatectomy					
	Patients, *n*	**3 years, %**	**4 years, %**	**5 years, %**	**6 years, %**	**7 years, %**	**Patients, *n***	**3 years, %**	**4 years, %**	**5 years, %**	**6 years, %**	**7 years, %**
Total patients	869	91	89	87	81	76	208	86	82	81	78	74
PSA, *ng/mL*												
0.0–4.0	254	94	94	94	90	90	70	97	97	97	97	97
4.1–10.0	474	92	89	87	81	76	104	84	82	78	78	65
10.0–20.0	104	87	82	73	64	64	25	66	66	66	66	66
≥ 20.0	34	62	62	62	62	NR	9	65	39	39	0	NR
Risk group												
Low	528	95	93	93	87	83	117	95	92	92	92	82
Intermediate	287	89	87	83	77	77	74	77	75	72	72	72
High	59	74	66	59	40	0	17	66	52	52	0	NR

NR—not reported; PSA—prostate-specific antigen.

Table 4. Cox regression results

Variable	Hazard ratio	95% CI	*P* value
Treatment	0.786 (brachytherapy:prostatectomy)	(0.51, 1.22)	0.338
Initial PSA, *ng/mL*	1.04 (per unit increase in ng/mL)	(1.02, 1.05)	< 0.0001
Gleason score	1.26 (per unit increase)	(1.09, 1.47)	0.002
Stage	2.42 (stage B:stage A)	(1.15, 5.11)	0.20
Prior hormones	0.748 (yes:no)	(0.49, 1.14)	0.172

CI—confidence interval; PSA—prostate-specific antigen.

treatment, initial PSA level, Gleason score, stage, and previous hormone therapy were used in the model. These results are presented in Table 4. The most significant variable was initial PSA level ($P < 0.0001$), with each ng/mL increase associated with an estimated 4% increase in recurrence hazard. Stage was also significant ($P = 0.020$), with stage B patients having about two times the hazard of stage A patients. Gleason score was also significant ($P = 0.002$), with each unit increase associated with an estimated 26% hazard increase. Use of hormone therapy was not significant at the conventional 0.05 level. We see no evidence that treatment group ($P = 0.285$) has any impact on recurrence. When hormone therapy was initiated we used Lupron and Eulexin for 3 months before the implant and 2 months following. We noted that the PSA level reached a nadir faster in the hormone group than in the nonhormone group, but over 6 years there was no difference in long-term survival [4,5]. None of the patients studied received adjuvant radiation therapy before or after seed implantation.

A different serum PSA endpoint is necessary for the brachytherapy and prostatectomy groups because no prostate tissue is left in the prostatectomy group. Therefore, a PSA level greater than 0.2 in the post-prostatectomy patient indicates recurrence. In the brachytherapy group, where prostate tissue remains in situ, our statistics show that when the PSA level is less than 1.5 ng/mL and not rising there is a statistical correlation with a negative biopsy at 2 years [4,5]. As we go beyond 3 to 5 years, most of our patients' PSA levels are less than 0.5 to 1.0 ng/mL, indicating the slowly persistent kill effect of the radioactive seeds on the remaining prostate tissue.

The 0.5 ng/mL PSA level nadir was achieved by 748 of the 869 brachytherapy patients (86%): 302 (35%) at 3 months, 295 (34%) at 1 year, 79 (9%) at 2 years, 37 (4%) at 3 years, 14 (2%) at 4 years, 10 (1%) at 5 years, 3 (< 1%) at 6 years, and 3 (< 1%) at 7 years. This same nadir was achieved by 206 of the 208 prostatectomy patients (99%): 186 (89%) at 3 months, 19 (9%) at 1 year, and 1 (< 1%) at 2 years. The 1.0 ng/mL nadir was achieved by 814 of the 869 brachytherapy patients (94%): 402 (46%) at 3 months, 343 (39%) at 1 year, 41 (5%) at 2 years, 18 (2%) at 3 years, 6 (1%) at 4 years, and 4 (<1%) at 5 or 6 years. For the prostatectomy patients the 1.0 ng/mL nadir was achieved by 206 of the 208 patients (99%): 186 (89%) at 3 months, 19 (9%) at 1 year, and 1 (<1%) at 2 years.

Discussion

Our results show equal or better Kaplan-Meier curves for freedom from recurrence across all preoperative serum PSA subsets of patients treated with brachytherapy compared with patients treated with radical prostatectomy. In general, results from retrospective studies must be viewed with some reservation, because they lack the rigor and controls afforded by prospective randomized studies. Selection bias is inherent in most of these studies. Clearly, patients in our study were not selected at random and data collection was controlled by what we had on file.

Other potential confounding factors include the fact that surgery and brachytherapy are not essentially comparable treatments; relapse was necessarily defined differently for the two groups; some subgroup sample sizes were extremely low; and follow-up time may be inadequate for this disease, in which recurrence often occurs many years after treatment. Since few practices have done brachytherapy for very long, few, if any, have extended follow-up for many patients. Nevertheless we feel that there is value to reporting our results thus far. Although we report the median follow-up for each treatment group to be 3 years, substantial numbers of patients have a greater amount of follow-up than this. Two hundred and twenty-nine brachytherapy and 53 prostatectomy patients were followed up for 5 years or more. Knowing this in advance, our rationale for performing this retrospective analysis was to test statistically what years of experience have indicated to us: that appropriately selected patients treated with brachytherapy have outcomes at least as good as those treated with surgery.

Much discussion in the literature has centered on nadir serum PSA after brachytherapy. Controversy continues over what nadir represents freedom from failure, and how comparable this nadir is to radical prostatectomy data. In our hands, our definition has withstood the test of time, and in fact our nadir gets lower with each postimplant year.

Our results conflict with the conclusions of D'Amico *et al.* [2]. He concluded that patients in the intermediate- and high-risk groups who underwent radical prostatectomy or external radiation fared better than those who

received implants. Upon review, however, his results present no biopsy data, and the length of follow-up after treatment was only 38 months. In our experience, it takes 30 to 36 months to reach a stable PSA level nadir after brachytherapy, and PSA levels may fluctuate until then. D'Amico *et al.* [2] used Kaplan-Meier curves to predict failure, and considered three consecutive increases in PSA level to represent treatment failure for all patients, even if the PSA level subsequently fell to less than 0.5 to 1.0 ng/mL. In addition, PSA levels are known to increase with cessation of hormonal therapy with Lupron, and therefore are not meaningful for 12 to 18 months after discontinuation of this agent. D'Amico *et al.* [2] defined biochemical failure as three consecutive increases in PSA levels at 3-month intervals. For example, according to his methods, PSA levels could increase from 0.5 ng/mL to 0.7 ng/mL to 1.0 ng/mL and be considered a biochemical failure, when in fact it is not. It is for this reason that biopsies are necessary. D'Amico *et al.* [2] measured eight PSA levels in the first 2 years of treatment, which because of more frequent measurements would be more likely to result in failure category.

Since 1993 we have treated 1074 patients with brachytherapy and 231 with prostatectomy. Treatment selection is based on the premise that each patient should have a minimum of 10 years of life expectancy. To help choose the most appropriate treatment, we evaluate patients based on the following:

1. The stage and extent of tumor, as determined by digital rectal exam and transrectal ultrasound
2. Prostate size and Gleason score
3. Patient age and life expectancy
4. Risk factors for postoperative complications, such as pretreatment voiding difficulty and degree of bladder outlet obstruction

In the absence of definitive evidence that one treatment for organ-confined disease will be superior to the other, the urologist discusses options with the patient. The advantages and disadvantages of surgery and radiation therapies are explained, and the patient is informed of the operative risks. The opportunity to avoid surgery is weighed against the benefit derived from removal of the prostate gland and the cancer, and an unbiased discussion of the estimated benefits and risks for the particular patient ensues. We encourage him to think carefully and come to his own decision. Thus, the patient is able to make a well-informed choice based on his own assessment of discussions with the urologist, the radiation oncologist, and his family.

Overall, complications have been experienced relatively infrequently by our patients. Our very preliminary estimated rate of incontinence with brachytherapy is less than 1% in the absence of a prior transurethral resection of the prostate, and less than 5% with a prior resection. The incidence of impotence is estimated to be 10% to 15% (depending on preoperative potency, when this information was available). Short-term morbidity is minimal; patients resume full activities 2 to 3 days after a 1-hour outpatient procedure. After prostatectomy, our very preliminary estimated incidence of incontinence and impotence is less than 1% and 45% respectively, rates that parallel those of leading centers. Despite the low number of surgery patients in this report, our safety data demonstrate sufficient experience and competence for a valid comparison of surgery and brachytherapy. We are presently conducting a prospective comparison of the incidence of incontinence and impotence after both treatments, results of which will be published upon completion of the analysis. Our current estimates come from chart reviews rather than any formal survey and are retrospective with all the inherent problems associated with reporting this type of data.

Conclusions

We believe that brachytherapy should be offered to patients with localized prostate cancer. This method should not be dismissed without an unbiased comparison of current results and complications of both brachytherapy and radical prostatectomy. Almost one decade of experience has convinced us that when patients are well selected, and the implant procedure is performed with meticulous attention to technique by experienced teams comprised of urologists, radiation oncologists, and radiation physicists, brachytherapy offers a cure rate as high as prostatectomy with a lower rate of complications. We use transperineal ultrasound-guided palladium-103 TheraSeed implants (Theregenics Corp., Buford, GA) for T1 and T2 prostate cancer patients. We have found this to be a minimally invasive treatment that produces results comparable with those of radical prostatectomy, and ultimately, continued excellent quality of life for the patient.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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