

## IMPACT OF SHORT COURSE HORMONAL THERAPY ON OVERALL AND CANCER SPECIFIC SURVIVAL AFTER PERMANENT PROSTATE BRACHYTHERAPY

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**Purpose:** To review the impact of prior hormonal therapy on 10-year overall and prostate cancer specific survival after primary brachytherapy.

**Methods and Materials:** A retrospective review was performed on the Arizona Oncology Services tumor registry for 2,378 consecutive permanent prostate brachytherapy cases from 1988 through 2001. Hormonal therapy was administered before the implant in 464 patients for downsizing of the prostate or at the discretion of the referring physician. All deceased patients with known clinical recurrence were considered to have died of prostate cancer, irrespective of the immediate cause of death. Risk groups were defined, with 1,135 favorable (prostate-specific antigen [PSA] < 10, Gleason < 7, Stage T1-T2a), 787 intermediate (single adverse feature), and 456 unfavorable (two or more adverse features) patients. Kaplan-Meier actuarial survival curves were generated for both overall and cause-specific survival from the time of treatment. Multivariate analysis was performed to assess the impact of hormonal intervention in comparison with known risk factors of grade, PSA, and age.

**Results:** With follow-up ranging up to 12.6 years and a median of 4.1 year, a total of 474 patients died, with 67 recorded as due to prostate cancer. Overall and cause-specific 10-year survival rates are 43% and 88%, respectively. Overall survival is 44% for the hormone naive patients, compared with 20% for the hormone-treated cohort ( $p = 0.02$ ). The cancer-specific survival is 89% vs. 81% for the same groups ( $p = 0.133$ ). Multivariate analysis confirms the significance of age > 70 years ( $p = 0.0013$ ), Gleason score  $\geq 7$  ( $p = 0.0005$ ), and prior hormone use ( $p = 0.0065$ ) on overall survival.

**Conclusions:** At 10 years, in prostate cancer patients receiving brachytherapy, overall survival is worse in men receiving neoadjuvant hormonal therapy, compared with hormone naive patients. This does not appear to be due to other known risk factors for survival (i.e., stage, grade, PSA, age) on multivariate analysis. The leading causes of death were cardiovascular, prostate cancer, and other cancers with no obvious discrepancy between the two groups. This finding is unexpected and requires confirmation from other centers. © 2004 Elsevier Inc.

Hormone therapy, Prostate cancer, Survival, Brachytherapy.

### INTRODUCTION

Men receiving external beam radiation therapy for prostate cancer are now commonly treated with neoadjuvant and adjuvant hormonal therapy. There have been numerous retrospective single institution reports suggesting benefit to the combination of androgen ablation and radiation therapy (1–4). A number of well-designed prospective multicenter trials have underscored the value of adding hormonal manipulation to standard radiation therapy and have shown improved cancer control rates (5) and a survival benefit (6) for patients so treated.

Ultrasound-guided brachytherapy for early-stage prostate cancer is now a standard treatment option for many patients. In one survey, Cooperberg *et al.* (7) report a sevenfold

increase in the frequency of brachytherapy administration as primary treatment between 1992 and 2001. In low-risk patients, they report that in 2001 fully 22% were treated with brachytherapy, rising to 31% in patients over 75 years of age. High response rates have been reported based on careful prostate-specific antigen (PSA) follow-up of brachytherapy series, and many such patients are considered cured of their disease, with long-term survival data comparable with surgical reports (8).

Since the introduction of transperineal techniques, androgen ablation has been used in selected cases to shrink the gland and avoid interference from the pubic arch. More recently neoadjuvant hormonal therapy has been integrated into brachytherapy treatment plans in the hopes that some of

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the improved results seen with external beam irradiation can also be achieved with brachytherapy. However, to date there are no compelling studies supporting this combination therapy, and its use remains an extrapolation from the external beam data. This study was performed to assess the value of hormone use in this setting using overall survival and cause-specific survival as endpoints.

## METHODS AND MATERIALS

Between December 1988 and December 31, 2001, 2,378 consecutive patients were treated at Arizona Oncology Services with brachytherapy for clinically localized prostate cancer. All were prospectively entered into an institutional tumor registry. This database and the patients' records were retrospectively reviewed under an Institutional Review Board–approved protocol in 2003.

All patients had biopsy-proven adenocarcinoma of the prostate, staged T1-T3, N0, M0. Central pathology review was not performed. Treatment consisted of ultrasound-guided transperineal permanent brachytherapy with  $^{125}\text{I}$  or  $^{103}\text{Pd}$ . Details of the technique changed significantly over the span of this review with the introduction of biplanar ultrasound, computed tomography (CT) based dosimetry and other innovations. The basic approach has previously been reported (9, 10) but is briefly as follows. All patients were preplanned with computerized dosimetry optimized to deliver 160 Gy over the lifetime decay of  $^{125}\text{I}$  (145 Gy after the introduction of TG-43) or 120 Gy over the lifetime of  $^{103}\text{Pd}$  (125 Gy after incorporation of NIST-1999) to the prostate with a 3–10 mm margin. Patients also receiving 45 Gy external beam irradiation were implanted with reduced doses of 120 Gy (110 Gy after TG-43) or 90 Gy (100 Gy after NIST-1999) for the two isotopes, respectively. Transperineal implantation was carried out as an outpatient procedure under spinal or general anesthesia with intraoperative ultrasound guidance utilizing afterloaded needles and the Mick Applicator (Mick Radio-Nuclear Instruments, Inc., Mount Vernon, NY).

Neoadjuvant hormone therapy was given to 464 men. An anti-androgen was added to the luteinizing hormone releasing hormone (LHRH) agonist in 226 patients. This was generally given for 3–6 months to reduce the size of the prostate, to avoid pubic arch interference, or at the discretion of the treating physicians. Frequently, the reasons for hormonal intervention were not spelled out in the record, particularly when treatment was instituted before the initial referral. The duration of androgen deprivation was 6 months or less in 80%, 6–9 months in 15%, 9–12 months in 2%, and more than 12 months in 3%. Hormonal treatment was not continued more than 3 months after implantation.

Before 1996, most patients received implant monotherapy. Subsequently, combination therapy with the addition of external beam was offered to 461 patients at the treating physician's discretion for high-risk features, such as PSA > 10, Gleason  $\geq$  7 or stage  $\geq$  T2b.

Patients were asked to return 3 months after treatment for PSA and DRE and were then typically seen every 3–4 months for the first year, every 6 months for the next 2 years, and annually thereafter. In the case of either out-of-state patients or restrictive insurance carriers, follow-up was achieved through referring physician notes or with the patients by phone or letter. Systematic follow-up biopsies were not performed. The Social Security Death Index, a national list of all Social Security recipients who have died, was accessed to ascertain patient status. The cause of death,

as recorded in the Arizona Department of Vital Records, was obtained from the Arizona State Cancer Registry and confirmed, when possible, through primary medical records.

Patients were stratified retrospectively in risk groups according to commonly accepted criteria. Favorable patients had no adverse risk factors of PSA > 10, Gleason Grade  $\geq$  7, or Stage  $\geq$  T2b. Intermediate risk patients exhibited one of these three risk factors. Unfavorable patients had two or more of these adverse findings.

For the purposes of analysis, death was considered due to prostate cancer in all patients who were reported to have died of prostate cancer, or those who died with any treated recurrence, even if not recorded as due to the cancer. An untreated rising PSA at the time of death was not alone considered as evidence of cancer death. Survival and cause-specific survival were calculated from the date of implantation.

Stepwise multivariate models were developed using Cox proportional hazards regression. Predictors of cause-specific and overall survival in both cases include Gleason Score, PSA value, stage value, and risk group levels. Graphical displays of the survival curves for predictor levels were produced using the actuarial method of Kaplan-Meier. Log-rank tests for the equality of survivor functions were made for each predictor with reference to cause-specific or overall survival.

## RESULTS

The median patient age was 73 years. Follow-up ranged from 0–12.6 years with a median of 4.1 years. At the time of presentation, the median PSA was 7.3 ng/mL. Details of the presenting characteristics of the study population are shown in Table 1 for the entire population and stratified for the 464 men who used neoadjuvant hormones. At the time of analysis, 1,297 patients are known to be alive and with no

Table 1. Presenting Characteristics

	All (n = 2378)	No hormones (n = 1884)	Hormones (n = 464)
Stage			
T1	870	653 (75%)	217 (25%)
T2a	974	809 (83%)	165 (17%)
T2b–T2c	518	417 (80%)	101 (20%)
T3	11	3 (27%)	8 (73%)
Gleason score			
2–4	335	290 (86%)	45 (14%)
5–6	1,457	1,197 (82%)	260 (18%)
7	445	321 (72%)	124 (28%)
8–10	116	56 (48%)	60 (52%)
PSA			
<4	305	252 (83%)	53 (17%)
4.1–10	1,454	1,185 (81%)	269 (19%)
10.1–20	468	340 (73%)	128 (27%)
>20.1	138	99 (72%)	39 (28%)
Risk group			
Favorable	1,135	956 (84%)	179 (16%)
Intermediate	787	606 (77%)	181 (23%)
Unfavorable	456	322 (71%)	134 (29%)
External beam			
Monotherapy	1,917	1,592 (83%)	325 (17%)
Combination	461	292 (63%)	169 (37%)

Abbreviation: PSA = prostate-specific antigen.

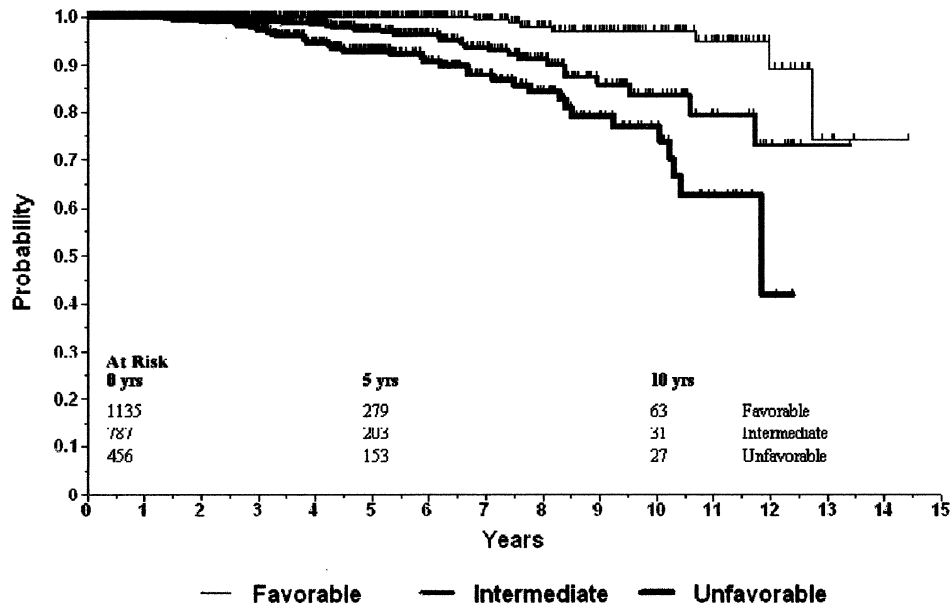


Fig. 1. Cause-specific survival is shown. At 10 years, cause-specific survival is 97% for the favorable risk group, 83% for the intermediate group, and 77% for unfavorable risk patients. Patients at risk are shown at the start, at 5 years, and at 10 years. All differences between curves are statistically significant ( $p < 0.003$ ).

evidence of disease, with another 161 alive with recurrent disease. A total of 474 patients are known to have died. Sixty-seven died of prostate cancer or after treatment for recurrent prostate cancer and 57 died with untreated recurrent cancer, as evidenced by only a rising PSA. Additionally, 333 died with no evidence of disease and 17 died of unknown cause.

Overall actuarial survival at 10 years is 43%. As the vast majority of deaths were due to causes other than prostate

cancer, the comparable cause-specific survival is 88% at 10 years. The risk of prostate cancer death is highly correlated with the initial risk group of the patient. As can be seen in Fig. 1, patients in the low-risk group had a 10-year cause-specific survival of 97% contrasted with a cause-specific survival of 77% for men with high-risk features ( $p = 0.003$ ).

Cause-specific survival is shown in Fig. 2 comparing the 464 patients who received neoadjuvant hormonal therapy

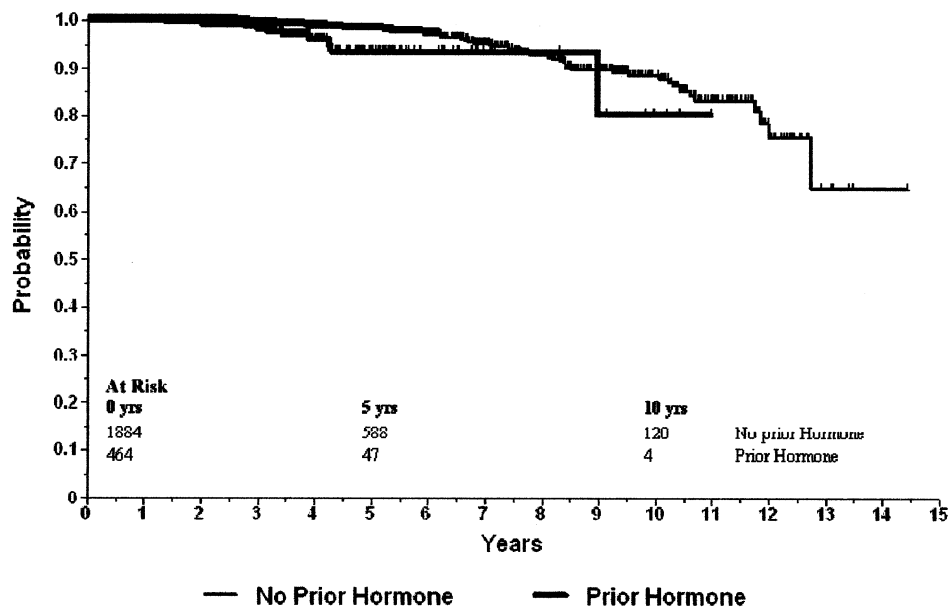


Fig. 2. Cause-specific survival is shown comparing patients who did not receive hormones with patients who were treated with neoadjuvant hormonal therapy. No significant difference is demonstrated for this endpoint ( $p = 0.133$ ).

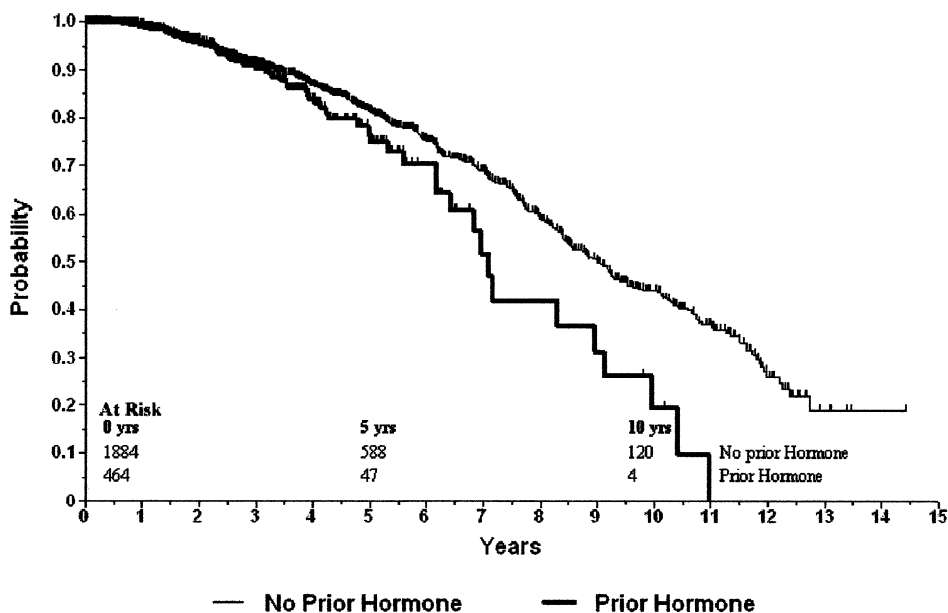


Fig. 3. Overall survival is compared for the patients not receiving hormones and patients who were treated with hormonal manipulation. At 10 years, survival is significantly better ( $p = 0.02$ ) for patients not receiving hormones (44%) vs. patients receiving neoadjuvant treatment (20%).

with the 1,884 men who received no hormone treatment. At 10 years, there is no statistically significant difference in cause-specific survival, with 89% and 81% for the two groups, respectively ( $p = 0.13$ ). This lack of benefit is seen in all three risk groups studied-favorable, intermediate, and unfavorable as well (data not shown). However, the overall survival is noted to be different for these two patient groups. The actuarial 10-year survival is 20% for the hormone-treated cohort and 44% for the untreated group ( $p = 0.02$ ) and is shown graphically in Fig. 3.

A stepwise multivariate analysis was performed for overall survival, looking at the independent risk factors thought to most likely confound the outcomes, namely age, Gleason score, baseline PSA, and hormone use. Not surprisingly, age ( $> 70$  years) and Gleason score ( $\geq 7$ ) were most highly correlated with survival. Hormone use was also found to be independently significant. However, PSA was not found to be an independent predictor of survival as shown in Table 2.

It is not obvious why hormone-treated patients have this increased risk. Cardiovascular disease was the single largest cause of death in both groups, with and without hormones, representing 24% and 22%, respectively, of the overall mortality. Prostate cancer caused 17% and 14% of the

overall deaths and other cancers accounted for 10% and 16% of deaths in these two groups. Pulmonary deaths were reported in 8% and 6%, respectively, while all other reported causes of death individually accounted for fewer than 5% of patient deaths.

### DISCUSSION

Radical surgery, external beam irradiation, and brachytherapy are all routinely offered to patients as definitive primary treatment for early-stage prostate cancer. Androgen deprivation hormone therapy has been extensively used in the palliative setting for advanced disease, and in selected early-stage patients who decline potentially curative treatments. However, there has been growing interest in combining hormonal intervention along with definitive therapies in an effort to improve cure rates.

Gleave *et al.* (11) have shown, in animal models, that hormonal treatment given before definitive cancer therapy, (neoadjuvant therapy), is superior to hormone treatment after treatment (adjuvant therapy). This finding has been further examined in cancer patients. In both retrospective and randomized trials, neoadjuvant therapy before radical prostatectomy, caused significant downstaging and reduced the risk of positive surgical margins (12, 13). However, there was no long-term benefit in cancer control rates. It has been suggested that a longer duration of therapy might be of benefit (12, 14); however, it is presently generally accepted that neoadjuvant treatment has only limited value before radical prostatectomy.

A number of well-controlled randomized trials assessing the value of hormonal therapy and external beam irradiation

Table 2. Multivariate analysis for survival

	T statistic	p Value
Age ( $>70$ )	3.22	0.0013
Gleason score ( $\geq 7$ )	3.48	0.0005
Hormone use	2.72	0.0065
PSA $>10$	1.04	0.2978

Abbreviation as in Table 1.

have been reported over the past 2 decades by the Radiation Oncology Therapy Group (RTOG). Early reports consistently showed improved freedom from recurrence as measured clinically (5, 15) or by PSA (16) endpoints across many subgroups. More recently, and with longer follow-up, improved overall survival has been shown in RTOG 86-10 for selected patients (17).

Similar results were shown by Bolla *et al.* (6). In a randomized study of 415 patients treated for locally advanced prostate cancer, hormone therapy instituted at the time of external beam radiotherapy and continued for 3 years, improved overall survival from 62% to 79% at 5 years. In an update (18) with median follow-up of 66 months, they document benefit in patients treated with hormones for all endpoints studied: local failure (16% vs. 2%), disease-free survival (40% vs. 74%), and cause-specific survival (79% vs. 94%).

Neoadjuvant hormonal therapy has been used along with prostate brachytherapy in an effort to shrink the prostate and avoid pubic arch interference. There are several published studies confirming the value of hormones in this setting (19, 20, 21). Others have used hormones with brachytherapy with the hope that they might improve outcomes in a manner analogous to patients receiving external beam irradiation. Looking at biochemical control, Sylvester *et al.* (22) suggested some benefit to the use of hormones in a small series. However, with longer follow-up this conclusion could not be supported (23). A prospective multicenter randomized trial using neoadjuvant hormones for intermediate and unfavorable brachytherapy patients was attempted in the 1990s, but was closed owing to poor accrual (24). Potters *et al.* (23), in a retrospective matched pair analysis, compared 132 patients who received neoadjuvant hormones and brachytherapy to 131 having brachytherapy alone. No difference in PSA relapse-free survival was seen with a median follow-up of 42 months. In a multivariate analysis, Merrick *et al.* (25) suggest slight improvement in the PSA endpoint only for the high-risk subgroup. In contrast, Stone *et al.* (26) have found benefit from the use of neoadjuvant hormones with brachytherapy. Routine biopsies performed 2 years after brachytherapy showed cancer in 14% of 181 patients who had no hormones compared with 3.5% of 115 men treated with neoadjuvant hormones. Five-year freedom from biochemical failure was 54% compared with 79% for the two groups (27). On multivariate analysis, they found hormone treatment to be the single most important predictor, when compared with dose, risk group, PSA, Gleason score, stage, and isotope.

The exact mechanism of action whereby hormones enhance the effect of radiation is not entirely clear. Consequently, it is difficult to predict whether the same survival benefit seen with external beam might be expected with brachytherapy. And with only single-institution studies and no prospective research, it is not unexpected that the brachytherapy literature is conflicting.

In conjunction with external beam, survival benefits have been primarily seen in men with higher risk features. Many

of these patients have risk factors not commonly found in brachytherapy patients. More than 90% of the men in the EORTC report and subsequent updates (18) had palpably bulky cancers ( $\geq T3$ ) and higher grade cancers. Patients in RTOG 86-10 had T3 cancers or PSAs ranging up to 560 ng/mL. These are clearly not the subset of patients usually referred for brachytherapy, and are distinctly more advanced than patients in the present study. However, Bolla (18) reports benefit to hormone use, even in those 10% who were reported as the "low-risk category." It should be noted, however, that this low-risk group is not defined the same as in the present study.

In a meta-analysis pooling four major RTOG studies assessing the value of hormones, Roach *et al.* (28) identified four risk groups and presented recommendations for the incorporation of hormones (29) in the treatment schema for external beam. All of our prostate brachytherapy population is contained within Groups 1 and 2 from that report, for which benefit from hormone therapy was least convincing. In fact, even Group 2 may represent a higher risk group of patients, as many T3 and node positive patients could still be within this group. Subsequent publication of RTOG 94-13 suggests that only patients who receive neoadjuvant hormones plus whole pelvic radiotherapy truly benefit from the additional treatment (15). Thus, it is not entirely surprising that our study fails to show any benefit on overall survival and cause-specific survival from the addition of hormonal treatments.

That the use of hormones cut the overall 10-year survival in half was unexpected in the present study. Similar results have not been previously published with LHRH agonists and antiandrogens. A review of Group 1 alone in the RTOG meta-analysis (29), did suggest an adverse effect of hormones, though data on this group alone have never been published (30). It remains entirely possible that some systemic effect of these drugs had a detrimental effect on overall survival. Such was the case in early studies of DES in prostate cancer where despite a therapeutic benefit, overall survival was diminished owing to excess cardiovascular deaths (31). Reviewing the reported cause of death for our patients, however, no single likely explanation can be identified for the excess deaths. The relative proportions for the most common causes appear to be roughly maintained.

Accelerated deaths were also reported in patients receiving 150 mg bicalutamide compared with placebo in the Early Prostate Cancer (EPC) trial program (32), and on that basis this treatment is no longer recommended for low-risk localized prostate cancer patients. This adverse effect was not seen in patients with more advanced local disease. These reports further support the hypothesis that patients suitable for permanent brachytherapy do not have sufficiently advanced disease to warrant the use of neoadjuvant hormones.

We conclude from these published studies that hormonal therapy improves survival in patients who are most at risk of dying of prostate cancer: men with undifferentiated tumors (i.e., Gleason 8-10) or large volume disease (i.e., T3, N+, or high PSA). In the majority of patients with early prostate

cancer, the natural history of the disease suggests a relatively lower risk of dying. For these patients, the risks of hormonal intervention may be greater than the small benefit that may accompany treatment.

By the very study design, the present data are subject to the limitations inherent with all single-institution retrospective studies. Hormones were administered over a 13-year period for a variety of uncontrolled reasons. Patients were treated for gland size reduction, for downstaging, and in some cases to allow patients to delay definitive treatment. Additionally, it is clear from the data that hormones were more commonly administered to unfavorable patients who were also more likely to receive combination therapy with external beam irradiation. This suggests a physician bias to offer hormonal intervention with the hope that the benefits seen in the external beam literature would also accrue to these brachytherapy patients. We are unable to control for these and other factors, and that may affect our endpoints. It is entirely possible that significant selection bias existed in other undefined ways as well. As a result, all such retrospective studies require confirmation from other centers with access to similar long-term survival data before any changes can be recommended in the routine management of this patient population. Prospective studies should be per-

formed to properly evaluate the value or risk of neoadjuvant hormonal intervention in the brachytherapy population. In the absence of specific data supporting the addition of hormones to brachytherapy, we urge caution in applying these combination therapies to patient populations for whom no benefit has been documented. Other than for reduction of the prostate size, there is still no clearly defined advantage to combining hormones with any brachytherapy procedure.

## CONCLUSION

Long-term cause-specific and overall survival rates for prostate brachytherapy are 88% and 43%, respectively, at 10 years. Cause-specific survival can be estimated from the risk group, using the stage grade and PSA. Favorable, intermediate, and unfavorable patients have cause-specific survivals of 97%, 83%, and 77%, respectively. The use of neoadjuvant hormonal therapy for up to 6 months provides no benefit in cause-specific survival and adversely affected the overall survival, with a reduction from 44% to 20%. This finding remains strongly significant on multivariate analysis. Confirmation is required from other series, and a prospective evaluation of hormones in the brachytherapy population is needed.

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