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National Practice Patterns and Time Trends in Androgen Ablation for Localized Prostate Cancer

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Abstract

Background—Recent reports have suggested that growing numbers of patients with localized prostate cancer are receiving androgen deprivation therapy as primary or neoadjuvant treatment, yet sparse clinical evidence supports the use of such treatment in some contexts. We describe national trends in the use of androgen deprivation therapy for localized disease and identify sociodemographic variables that are associated with its use.

Methods—CaPSURE™ is an observational database of 7195 patients with prostate cancer. For this study, 3439 of these patients were included who were diagnosed since 1989, had clinical staging information available, and were treated with radical prostatectomy, radiation therapy, or primary androgen deprivation therapy (PADT). High-, intermediate-, or low-risk groups were defined by serum prostate-specific antigen level, Gleason sum, and clinical tumor stage. Time trends in use of PADT and neoadjuvant androgen deprivation therapy (NADT) were analyzed, and a multivariable logistic regression model was used to identify sociodemographic factors associated with various treatments. All statistical tests were two-sided.

Results—Rates of PADT use have risen sharply from 4.6% to 14.2%, 8.9% to 19.7%, and 32.8% to 48.2% (all $P<.001$) in low-, intermediate-, and high-risk groups, respectively. NADT use likewise has increased in association with radical prostatectomy (2.9% to 7.8% of patients, $P = .003$) and external-beam radiotherapy (9.8% to 74.6%, $P<.001$) across all risk levels combined. Rates among patients treated with brachytherapy also have risen but the rise was not statistically significant. (7.4% to 24.6%, $P = .100$).

Conclusions—Rates of both PADT and NADT are increasing across risk groups and treatment types. Additional clinical trials must define more clearly the appropriate role of hormonal therapy in localized prostate cancer, and future results should shape updated practice guidelines.

INTRODUCTION

Androgen deprivation has been an essential tool in the armamentarium of physicians treating prostate cancer since Huggins and Hodges (1) reported their seminal findings on hormonal manipulation of prostate carcinoma cells. The role for hormonal therapy initially was restricted to men with advanced, inoperable disease. In the era of prostate-specific antigen (PSA) screening, however, earlier detection and downward stage migration have been accompanied by a proliferation of treatment alternatives; patients may now receive androgen deprivation earlier in the course of the disease, as either primary or neoadjuvant treatment.

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Although recent studies have confirmed the value of hormonal therapy in advanced disease (2), the appropriate role for primary androgen deprivation therapy (PADT) in localized prostate cancer has not been well-defined. No controlled trials have compared this approach to watchful waiting or other definitive therapies; indeed, the American Urological Association's clinical practice guidelines consider PADT to be investigational in localized disease (3). In their recent analysis from the Prostate Cancer Outcomes Study, however, Potosky et al. (4) reported that 12.5% of the men in the study had received PADT, expressed their surprise that over half of these patients had presented with localized disease, and suggested further that PADT use in this context had increased since their analysis.

Neoadjuvant androgen deprivation therapy (NADT) has been evaluated as a means of down-staging tumors and potentially eradicating micrometastatic disease at the onset of treatment. For patients treated with radical prostatectomy (RP), NADT aims to increase the likelihood that a given cancer will be organ-confined at the time of resection, because positive surgical margins are associated with higher rates of treatment failure at 5 years (5,6). No study, however, has yet shown a survival benefit or an improvement in surrogate end points, such as PSA-defined recurrence (7–11).

For patients receiving external-beam radiotherapy (EBRT), good evidence supports the addition of NADT in locally advanced or high-risk disease (12–14); trials are still ongoing in patients with localized, lower-risk disease. NADT has also been used to shrink large prostate glands before brachytherapy via the induction of apoptosis in susceptible cells; such cytoreduction facilitates implantation from a technical perspective but has not been shown to influence outcomes (15). A recent single-institution study of patients treated between 1995 and 1999 found that brachytherapy patients were in fact the most likely to receive NADT (51% of brachytherapy patients, 33% of EBRT patients, and 28% of RP patients) (16).

The appropriate role of hormonal therapy in localized prostate cancer remains to a large extent an open question, and a need exists to document evolving practice patterns and the extent to which they are associated with emerging evidence for and against the use of hormonal ablation. We therefore present national trends in the use of PADT and NADT and analyze clinical and demographic factors associated with the use of hormonal therapy.

METHODS

Description of data registry

CaPSURE™ (Cancer of the Prostate Strategic Urologic Research Endeavor) is a longitudinal, observational database of men with biopsy-proven prostate adenocarcinoma, recruited from 35 academic- and community-based urology practices across the United States. The database was established in 1995 to study national trends in oncologic, health-related quality of life, and economic outcomes of prostate cancer treatment. All patients with prostate cancer were recruited consecutively by participating urologists, who report complete clinical data and follow-up information on diagnostic tests and treatments. Data for patients diagnosed before 1995 but still followed by a urologist were initially entered retrospectively; for those diagnosed since 1995, all data entry has been prospective. Written informed consent is obtained from each patient under local institutional review board supervision. Patients are treated according to their physicians' usual practices and are followed until time of death or withdrawal from the study. Completeness and accuracy of the data are assured by random sample chart review every 6 months. Additional details of the project methodology have been reported previously (17).

Subjects

As of August 2001, 7379 patients were invited to participate, and 7195 (97.5%) agreed. We studied patients diagnosed since 1989 (n = 6411) who received as primary therapy RP, EBRT, brachytherapy, PADT, or watchful waiting. We excluded 1012 patients because they had incomplete clinical staging information (PSA, Gleason sum, and clinical tumor stage) at the time of accession and 400 patients because their primary treatment was missing or unknown; 161 patients who received cryotherapy as primary treatment also were not analyzed. Although treatment outcomes were not assessed in this study, we required at least 180 days of follow-up after primary treatment to distinguish hormonal ablation intended as primary treatment from NADT given before definitive treatment. There were 1399 patients who did not meet this follow-up criterion; the remaining 3439 patients in the database constituted the dataset for analysis.

Data abstraction

Demographic factors extracted from CaPSURE included age at diagnosis, ethnicity, education, income, site location and type (academic or community), and insurance type. Clinical factors included serum PSA level at diagnosis, Gleason score of diagnostic biopsy examination, and pre-treatment clinical tumor stage. Risk groups were based on the following factors: low-risk patients were defined as those with a PSA level of 10.0 ng/mL or less, a Gleason sum of 6 or less, and a clinical stage of T1 or T2a; intermediate-risk patients were those with a PSA level of 10.1–20.0 ng/mL, a Gleason sum of 7, or a clinical stage of T2b; and high-risk patients were those with a PSA level of 20.0 ng/mL or more, a Gleason sum of 8–10, or a clinical stage of T3 or T4 (18).

Primary treatments were reported by CaPSURE physicians as watchful waiting, RP, EBRT, brachytherapy, or PADT. Patients were considered to have received NADT if their primary treatment was reported as “prostatectomy with neoadjuvant therapy” or “radiotherapy with neoadjuvant therapy” or if their primary treatment was reported as “hormonal therapy” but they received a definitive secondary treatment (RP, EBRT, or brachytherapy) within 180 days of primary treatment. Two parallel sets of cross-sectional analyses were performed. The first examined the proportion of patients who received PADT compared with other primary treatments. The second examined the proportion of all patients undergoing definitive local treatment (RP, EBRT, or brachytherapy) who first received NADT.

Statistical analysis: time trends and factors associated with utilization

Trends in utilization rates were assessed by plotting percentage of patients in each group receiving hormonal therapy against each year of diagnosis. The slopes of the trends were estimated by linear regression analysis weighted by number of patients in each year and, for the neoadjuvant therapy analysis, within each primary treatment group. For the PADT regression analysis, the data were analyzed by risk groups; there were insufficient numbers of patients in each group in each year to do the same in the NADT analysis. Of note, CaPSURE underwent a structural transition in 1998, and although the data before and after this time are fully comparable, overall accrual in that year was only 50 patients. Although the regression analyses were weighted to compensate for year-to-year variation in sample size, the low numbers in 1998 distorted the plots; therefore, 1998 data were combined with 1999 in plotting individual years. Statistical significance of the temporal trends was assessed with the Mantel-Haenszel χ^2 test for trend.

Demographic and clinical factors associated with the use of hormonal therapy were first assessed in a univariate analysis with the χ^2 test for categorical variables (ethnicity, location, practice type, and type of insurance) and the Mantel-Haenszel χ^2 test for ordinal and categorized continuous variables (risk, education, income, and age). Factors associated with

hormone use at a univariate probability (*P*) value of less than .1, including year of diagnosis, were further analyzed in a backward selection logistic regression model, and *P* values were determined from the Wald χ^2 score for each variable. Because the distribution of patients among risk groups has changed over time (19,20), we also included in the analysis the interaction term (year of diagnosis × risk group), which was not statistically significant in either the PADT model (*P* = .199) or the NADT model (*P* = .133). Univariate and multivariable odds ratios (OR) with 95% confidence intervals (CI) were also calculated.

For the multivariable analysis, 881 patients with no income or education data were excluded; a reanalysis of the model that excluded these variables, however, confirmed that the exclusion of these patients did not change the results for any other variable. Utilization frequencies at the various levels of the variables with statistically significant multivariable results were compared by use of Tukey's multiple comparisons analysis. All tests of statistical significance were two-sided. All analyses were performed with SAS software, version 8.2 (The SAS Institute, Cary, NC).

RESULTS

Patient characteristics

Clinical and demographic characteristics of the patients in each primary treatment group are presented in Table 1. The mean age at diagnosis was 67.7 years (standard deviation [SD] = 8.2 years). The mean and median serum PSA levels were 16.8 ng/mL (SD = 22.1) and 8.7 ng/mL, respectively. The median biopsy Gleason score was 6. Roughly one-third of the patients fell into each risk group.

Time trends in use of hormonal therapy

Primary treatment practice patterns over time in low-, intermediate-, and high-risk patients are shown in Fig. 1. Rates of PADT use have risen sharply, from 4.6% to 14.2%, 8.9% to 19.7%, and 32.8% to 48.2% (all *P*<.001) in low-, intermediate-, and high-risk groups, respectively. NADT use likewise has increased in association with radical prostatectomy (2.9% to 7.8% of patients, *P* = .003) and external-beam radiotherapy (9.8% to 74.6%, *P*<.001) across all risk levels combined, with roughly 5-, 4-, and 2-fold increases in low-, intermediate-, and high-risk RP patients, respectively, and 10-, 15-, and 6-fold increases in EBRT patients, as shown in Table 2. NADT use in brachytherapy patients increased as well but the increase was not statistically significant (7.4% to 24.6%, *P* = .100); however, rates among these patients have been more variable than those among RP or EBRT patients, in part because of the changing patterns of brachytherapy use over time. During the first 10 years of the study, the proportion of men undergoing brachytherapy increased gradually from 3.4% to 5.3%, but, in the last 3 years, the rate jumped to 13.1%, with sharp increases in the rates for low- and intermediate-risk patients and a decrease in the rate for high-risk patients.

Fig. 2 shows time trends in the rates of PADT use by individual years. The increasing trends are all statistically significant and are similar across the three groups, although the absolute increase is greatest in the high-risk group (5.4% to 62.5%). Trends in the use of NADT use in RP, EBRT, and brachytherapy patients are shown in Fig. 3. Rates among patients receiving EBRT have risen consistently and rapidly over the study period. The rates of increase among RP and brachytherapy patients have been less consistent and less marked; the increase among brachytherapy patients is not statistically significant.

Factors associated with hormonal therapy

Demographic and clinical factors associated with hormonal treatment are shown in Table 3. By univariate analysis, year of diagnosis, risk, age, geographic location, education, and income were all statistically significantly associated with PADT use. Year of diagnosis, risk, age, and geographic location persisted in the multivariable analysis. Patients with intermediate and low risk disease were 1.6 (CI 1.1 to 2.1) and 6.0 (CI 4.5 to 8.0) times as likely, respectively, to receive PADT relative to low risk patients. Subgroup analysis of the three risk groups revealed that the PSA level, Gleason score, and clinical tumor stage were independently associated with PADT use for high-risk patients only; none of the three factors were associated with PADT use for low-risk patients, and only the Gleason score was associated with PADT for intermediate-risk patients.

Multiple comparisons analysis on those variables with statistically significant results in the multivariable model yielded the following results: the differences among the three risk groups were statistically significant. Patients older than 80 years of age had the highest rates of PADT use (OR 5.9, CI 3.6 to 8.5 relative to those under 60), followed by those 70–79 years old (OR 2.0, CI 1.4 to 2.9), and finally those younger than 70 years. Patients treated in the South or West were more likely to receive hormones as primary treatment than those in the East or Midwest. Patients with an annual income of $10,000 or less had higher rates of PADT use than those with annual incomes of more than $30,000.

In univariate analysis, NADT use was statistically significantly associated with year of diagnosis, risk, age, location, practice type, and income; location and income did not persist in the multivariable model. Patients with intermediate and low risk disease were 1.7 (CI 1.2 to 2.5) and 4.6 (CI 3.1 to 6.8) times as likely, respectively, to receive PADT relative to low risk patients Multiple comparisons indicated that patients older than 80 years of age were more likely to receive NADT than those younger than 70 years of age, as were patients treated in academic practices. Those with Veterans Affairs health coverage had lower rates of utilization than those with Medicare coverage (OR 0.1, CI 0.0 to 0.5). Income again tended toward a statistically significant association, with those earning $10,000 or less per year the most likely to receive NADT (OR for all other income levels 0.3 to 0.5). In an analysis by local treatment type, the higher utilization rates for NADT in the academic practices (OR 3.5, CI 2.2 to 5.4) were fully explained by EBRT patients (59.7% for EBRT patients vs. 25.4% for those in the community); the difference was not statistically significant for other primary treatments. The only factors that were consistently present on subgroup analysis of each primary treatment type were risk group and year of diagnosis.

DISCUSSION

Androgen deprivation exerts potent *in vivo* antitumor effects in prostate cancer (21,22). Like other prostate cancer treatments, however, hormonal ablation may also cause a range of short- and long-term side effects, which in the setting of monotherapy have been demonstrated to have a statistically significant impact on health-related quality of life relative to watchful waiting (4,23). The combination of NADT with EBRT or brachytherapy is likewise associated with impairment of some quality of life domains relative to either treatment alone (16). Furthermore, Penson et al. (24) demonstrated that stage for stage, the combination of NADT with RP or EBRT is the most expensive treatment alternative for prostate cancer, regardless of which primary treatment (RP or EBRT) is used.

PADT remains the mainstay of treatment for advanced disease: a large, recent trial (2) found a statistically significant benefit for immediate versus deferred treatment of locally advanced or metastatic prostate cancer. However, PADT has only recently been studied in localized disease. Labrie et al. (25) tested primary combined androgen blockade in 141 patients with

stage T2-3 disease who refused or were ineligible for local treatment. Disease-free survival rates among the stage T3 patients were 74.6% and 53.8% at 5 and 10 years, respectively; the disease of only one stage T2 patient progressed. Azaka et al. (26) likewise treated 151 patients with stage T1-3a prostate cancer with PADT, again selecting patients ineligible for or refusing definitive treatment. They reported a 2-year progression-free survival of 43% and 62%, respectively, in stage T2b patients treated with a luteinizing hormone-releasing hormone agonist alone and with combined androgen blockade; rates were similar among T3 patients. Although these reports suggest a potential role for PADT, both studied highly selected patients, and neither compared PADT with watchful waiting, placebo, or other treatment alternatives. In a recent critical evaluation of hormonal therapy for prostate cancer, Chodak et al. (27) concluded that there is insufficient evidence to support androgen deprivation as monotherapy in localized disease.

We found that rates of PADT in high-risk patients were stable—just under 50%—over the past 5 years. However, rates among low- and intermediate-risk patients increased sharply, from 4.6% to 14.2% and from 8.9% to 19.7%, respectively. Overall, patients were nearly three times as likely to receive PADT from 1999 through 2001 as they were from 1989 through 1992. Any explanation for this trend is speculative, but it seems likely that many patients who may have opted for watchful waiting earlier are now choosing PADT, perhaps in the face of earlier and more frequent PSA testing.

We found strikingly higher rates of PADT use among low-income patients. In the short term (the first year of treatment), PADT is the least expensive treatment alternative for primary prostate cancer (24), but income was also inversely associated with the likelihood of receiving NADT, the most costly alternative. Furthermore, uninsured patients were not more likely than insured patients to receive PADT (14.9% vs. 20.5%, $P = .34$ by χ^2 test) and were more likely than insured patients to receive NADT (25.5% vs. 9.1%, $P<.001$ by χ^2 test). Although lower income patients had a higher level of serum PSA ($P<.001$), a higher Gleason sum ($P<.001$), and a higher tumor stage ($P = .03$, all by Mantel-Haenszel χ^2), income was statistically significantly associated with the use of PADT, despite adjustment for risk: among low-risk patients, 19.4% of those earning less than $10,000 annually received PADT compared with 7.4% of those earning more than $75,000 annually. There is no readily apparent explanation for these observations, and so we urge that the question of socioeconomic determinants of hormonal therapy be subjected to more focused testing in the future.

We found that, since 1996, overall rates of NADT use among RP patients rose gradually, particularly among high-risk patients, of whom 16% received NADT before surgery. Although a survival advantage for immediate adjuvant hormonal therapy has been observed when lymph node involvement is found at the time of prostatectomy (29), recent data do not support androgen ablation in this neoadjuvant setting. Randomized trials over the past decade, studying a variety of regimens before RP, have consistently shown decreases in preoperative PSA levels, tumor volume, positive margin rates, and pathological stage; however, none has shown any advantage in terms of PSA-defined recurrence or survival (7–9,30).

Soloway et al. (10) published the 5-year follow-up results from a multi-center trial in patients with clinical stage T2b prostate cancer. Their findings confirm the earlier studies that NADT decreased the positive margin rate from 48% to 18% ($P<.001$) but had no impact on lymph node involvement or on 5-year PSA-defined recurrence-free rates (64.8% in the NADT group compared with 67.6% in the RP only group, $P = .663$). Aus et al. (11) recently reported similar outcomes at 7 years of follow-up, with no difference in progression-free survival (49.8% for NADT compared with 51.5% for RP only, $P = .588$). Studies of

prolonged NADT (8 months rather than 3 months before surgery) have suggested a greater effect in terms of preoperative and pathologic parameters (31); outcomes in terms of recurrence, however, are pending. Chodak et al. (27) argued that sufficient evidence currently exists to recommend against NADT before RP.

Rates in CaPSURE of NADT use before EBRT rose to 57%, 74%, and 90% of low-, intermediate-, and high-risk patients. Available evidence in fact demonstrates a clear benefit for this combined regimen in selected patients. In a multicenter randomized trial enrolling primarily patients with T3 or T4 prostate cancer, Bolla et al. (12) found a statistically significant overall survival advantage with the addition of goserelin to EBRT (79% vs. 62% for EBRT alone, $P = .001$). Two prospective trials from the Radiation Therapy Oncology Group confirmed the benefit in high-risk disease. In the RTOG 85-31 study, 977 patients were randomly assigned to EBRT with or without combined androgen blockade, and at the 4.5-year follow-up for patients with stage T3 or lymph node-positive tumors, improvements with NADT in terms of PSA-defined recurrence (16% vs. 29%, $P<.001$) and disease-specific survival (60% vs. 44%, $P<.001$) were observed. Overall survival was only improved among patients with Gleason scores of greater than 7 (66% vs. 55%, $P = .03$) (13).

In the RTOG 86-10 study, 471 patients with stage T3 or bulky (>25 cc) stage T2 tumors were randomly assigned to goserelin given 2 months before EBRT or to EBRT alone. With 8.6 years of follow-up, a benefit was demonstrated for NADT with respect to local control (42% vs. 30%, $P = .016$), PSA-defined recurrence (76% vs. 90%, $P<.001$), and disease-free survival (33% vs. 21%, $P = .004$). In contrast to RTOG 85-31, however, an overall survival benefit was demonstrated only in patients with Gleason scores less than 7 (70% vs. 52%, $P = .015$) (14). Intermediate- and high-risk patients planning to undergo EBRT are the only localized prostate cancer patients for whom Chodak et al. (27) found sufficient evidence to recommend routine NADT. No study has reported an advantage for EBRT with NADT in patients with lower-risk disease. The ongoing RTOG 94-08 and RTOG 94-13 studies will address this issue, as will a Canadian Uro-Oncology Group trial that is randomly assigning patients to EBRT with NADT or to hormonal therapy alone (32).

Roughly one-quarter of patients undergoing brachytherapy received NADT before implantation. Although this combination is recommended by the American Brachytherapy Society for patients with a prostate volume of greater than 60 cm^3 and those with a "significant risk of disease outside the implant volume"(33), its efficacy and toxicity have not been evaluated in randomized trials. In one retrospective study, Potters et al. (15) analyzed 612 consecutive patients with prostate cancer undergoing brachytherapy, of whom 177 (29%) were treated with NADT before implantation because of a large prostate volume. Of these, 71% were effectively cytoreduced within 3 months, and 91% were cytoreduced by 8 months of therapy. However, when compared with risk-matched patients receiving brachytherapy only, 5-year PSA-defined recurrence-free rates were essentially identical: 87.1% and 86.9% in the NADT and brachytherapy-only groups ($P = .935$). Subgroup analysis did not identify any benefit for patients with specific risk characteristics, nor did NADT improve outcomes in patients receiving EBRT along with brachytherapy.

Potters et al. (15) concluded that the addition of NADT to brachytherapy should not be considered standard treatment, but that the cytoreductive effect of androgen ablation may decrease the toxicity associated with brachytherapy and potentially can improve dosimetry. In a follow-up study (34), however, they noted that patients who received NADT before brachytherapy had a 5-year actuarial potency rate of 52% compared with 76% for those who did not receive NADT. The effect of NADT was stronger than that of age or concurrent EBRT. Chodak et al. (27) found insufficient evidence to support this treatment combination. Because CaPSURE physicians submitting data on brachytherapy patients do report the

preimplantation prostate volume, we cannot determine whether the volume was measured before or after NADT. Therefore, we cannot comment as to whether large prostate volumes or other clinical parameters are the more common determinants of NADT use in our population.

One of the great strengths of CaPSURE is that it tracks use and outcome patterns in actual practice, without the constraints imposed by clinical trial protocols. Data are collected prospectively, irrespective of any particular research question. Although the CaPSURE practice sites have not been chosen at random and, thus, cannot be assumed to represent a statistically valid sample of the United States patient population, they do represent a broad range of geographic locales and a mixture of academic and community practices. CaPSURE data are submitted only by patients and urologists; therefore, any treatments by other practitioners that are not reported by patients either to their urologists or in their questionnaires may be missed. Extant quality assurance mechanisms, including chart review of all hospital admissions, should minimize this problem. Finally, we excluded from analysis 1399 (28.9%) of 4838 otherwise eligible patients in the database because they had not yet had at least 6 months of follow-up. This criterion was established *a priori*, and we do not have reason to believe it introduced bias into the analysis. It is, however, possible that, with longer follow-up, the distribution of treatments, particularly for the most recent time period, may change. Despite these cautionary notes, we believe our data provide the best available description of national practice patterns.

PADT remains the core treatment for advanced prostate cancer and offers a clear benefit in specific local disease contexts. Like other treatments, however, both PADT and NADT contribute appreciably to patient morbidity, quality of life impact, and cost of care. It is not clear from evidence to date that the growing numbers of patients opting for PADT—who tend to be older and at high risk in terms of comorbidity—are likely to reap a substantial benefit, especially given the need for prolonged therapy. Extant evidence likewise does not appear to support NADT before RP or brachytherapy, and only upholds NADT before EBRT in locally advanced disease. Nonetheless, burgeoning numbers of patients with localized disease of low- and intermediate-risks are increasingly receiving both PADT and NADT. The extent to which these trends are driven by physicians, patients, or both is a question of speculation, although a multifactorial explanation seems the most likely that plausibly includes physician financial incentives, direct-to-consumer pharmaceutical advertising, and psychological imperatives on one or both sides of the examining table—to treat cancer as aggressively as possible.

The benefits of androgen ablation in advanced prostate cancer are well demonstrated, and we hope that the upward trend in use of NADT in the context of EBRT for locally advanced disease will continue. However, prospective clinical trials must clarify the efficacy of PADT compared with watchful waiting, and must identify any potential benefit to be gained from NADT in association with brachytherapy or EBRT in lower-risk disease, particularly as new agents and regimens emerge. Such trials must assess quality of life and oncologic outcomes. Updated clinical guidelines that are based on available evidence are sorely needed; these guidelines should address the optimal role of both PADT and NADT in the initial management of localized prostate cancer.

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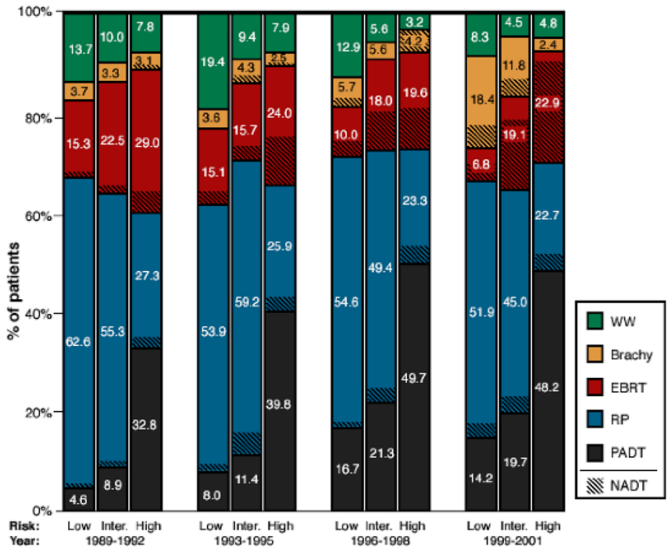

Fig. 1.

Overall trends in primary treatments for prostate cancer. Within each time period (1989–1992, 1993–1995, 1996–1998, and 1999–2001), data are presented by clinical risk group. Each number on the graph refers to the total percentage of patients in each time and risk group receiving a given primary treatment: watchful waiting (WW), brachytherapy (Brachy), external-beam radiotherapy (EBRT), radical prostatectomy (RP), and primary androgen deprivation therapy (PADT). Within the Brachy, EBRT, and RP bars, cross-hatched areas represent patients receiving neoadjuvant androgen ablation therapy (NADT) before local treatment.

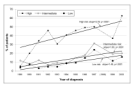

Fig. 2.

Time trends in the use of primary hormonal therapy. Regression lines for low-, intermediate-, and high-risk patients are weighted at each year by total number of patients in that year. As discussed above, patients in 1998 were merged with 1999 because of the low total accrual to CaPSURE in 1998. Slopes are presented for the regression lines. *P* values are determined by the two-sided Mantel-Haenszel χ^2 test for trend.

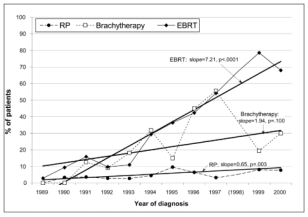

Fig. 3.

Time trends in the use of neoadjuvant hormonal ablation. Regression lines for radical prostatectomy (RP), brachytherapy, and external-beam radiotherapy (EBRT) patients are weighted at each year by total number of patients in that year in each treatment group. As discussed above, patients in 1998 were merged with 1999 because of the low total accrual to CaPSURE in 1998. Slopes are presented for the regression lines. *P* values are determined via the two-sided Mantel-Haenszel χ^2 test for trend.

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Table 1

Patient demographic and clinical characteristics

	Watchful waiting (n = 348)		Radical prostatectomy (n = 1588)		External-beam radiotherapy (n = 626)		Brachytherapy (n = 175)		PADT* (n = 702)		Overall (n = 3439)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Age at diagnosis												
<60 y	16	(4.6)	459	(28.9)	36	(5.8)	7	(4.0)	63	(9.0)	581	(16.9)
60-69 y	99	(28.4)	855	(53.8)	184	(29.4)	69	(39.4)	176	(25.1)	1383	(40.2)
70-79 y	188	(54.0)	273	(17.2)	370	(59.1)	92	(52.6)	340	(48.4)	1263	(36.7)
≥ 80 y	45	(12.9)	1	(0.1)	36	(5.8)	7	(4.0)	123	(17.5)	212	(6.2)
Ethnicity												
Caucasian	302	(86.8)	1361	(85.7)	538	(85.9)	160	(91.4)	586	(83.5)	2947	(85.7)
African-American	34	(9.8)	171	(10.8)	73	(11.7)	3	(1.7)	83	(11.8)	364	(10.6)
Latino	4	(1.1)	30	(1.9)	6	(1.0)	9	(5.1)	13	(1.9)	62	(1.8)
Other	8	(2.3)	26	(1.6)	9	(1.4)	3	(1.7)	20	(2.8)	66	(1.9)
PSA*												
< 4.0 ng/mL	57	(16.4)	222	(14.0)	39	(6.2)	22	(12.6)	40	(5.7)	380	(11.1)
4.0–10.0 ng/mL	170	(48.9)	881	(55.5)	268	(42.8)	103	(58.9)	195	(27.8)	1617	(47.0)
10.01–20.0 ng/mL	76	(21.8)	327	(20.6)	161	(25.7)	33	(18.9)	144	(20.5)	741	(21.6)
> 20.0 ng/mL	45	(12.9)	158	(9.9)	158	(25.2)	17	(9.7)	323	(46.0)	701	(20.4)
Gleason sum												
2–4	116	(33.3)	275	(17.3)	91	(14.5)	28	(16.0)	46	(6.6)	556	(16.2)
5–6	167	(48.0)	945	(59.5)	281	(44.9)	108	(61.7)	271	(38.6)	1772	(51.5)
7	45	(12.9)	278	(17.5)	148	(23.6)	26	(14.9)	201	(28.6)	698	(20.3)
8–10	20	(5.7)	90	(5.7)	106	(16.9)	13	(7.4)	184	(26.2)	413	(12.0)
Clinical tumor stage												
T1	132	(37.9)	375	(23.6)	140	(22.4)	44	(25.1)	150	(21.4)	841	(24.5)
T2	191	(54.9)	1167	(73.5)	406	(64.9)	127	(72.6)	411	(58.5)	2302	(66.9)
T3	21	(6.0)	45	(2.8)	76	(12.1)	4	(2.3)	126	(17.9)	272	(7.9)

	Watchful waiting (n = 348)		Radical prostatectomy (n = 1588)		External-beam radiotherapy (n = 626)		Brachytherapy (n = 175)		PADT* (n = 702)		Overall (n = 3439)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
T4	4	(1.1)	1	(0.1)	4	(0.6)	0	(0.0)	15	(2.1)	24	(0.7)
Risk group												
Low	179	(51.4)	654	(41.2)	151	(24.1)	78	(44.6)	117	(16.7)	1179	(34.3)
Intermediate	100	(28.7)	674	(42.4)	225	(35.9)	67	(38.3)	174	(24.8)	1240	(36.0)
High	69	(19.8)	260	(16.4)	250	(39.9)	30	(17.1)	411	(58.5)	1020	(29.7)
Insurance type												
Medicare only	77	(22.1)	240	(15.1)	158	(25.2)	36	(20.6)	151	(21.5)	662	(19.3)
Medicare/supplemental	246	(70.7)	1258	(79.2)	430	(68.7)	132	(75.4)	517	(73.6)	2583	(75.1)
Veterans affairs	13	(3.7)	63	(4.0)	32	(5.1)	2	(1.1)	18	(2.6)	128	(3.7)
Other	12	(3.4)	27	(1.7)	6	(1.0)	5	(2.9)	16	(2.3)	66	(1.9)
Geographic region												
West	85	(24.4)	212	(13.4)	75	(12.0)	29	(16.6)	148	(21.1)	549	(16.0)
East	137	(39.4)	792	(49.9)	343	(54.8)	44	(25.1)	240	(34.2)	1556	(45.3)
Midwest	54	(15.5)	193	(12.2)	77	(12.3)	30	(17.1)	79	(11.3)	433	(12.6)
South	72	(20.7)	391	(24.6)	131	(20.9)	72	(41.1)	235	(33.5)	901	(26.2)
Site type												
Community	303	(87.1)	1471	(92.6)	542	(86.6)	168	(96.0)	642	(91.5)	3126	(90.9)
Academic	45	(12.9)	117	(7.4)	84	(13.4)	7	(4.0)	60	(8.5)	313	(9.1)
Education†												
Grade school	28	(9.7)	76	(5.5)	48	(9.0)	10	(6.8)	61	(10.4)	222	(7.6)
Some high school	49	(16.9)	152	(11.0)	69	(12.9)	24	(16.3)	89	(15.2)	383	(13.0)
High/tech school	74	(25.5)	362	(26.1)	150	(28.0)	29	(19.7)	154	(26.4)	769	(26.1)
Some college	54	(18.6)	263	(18.9)	86	(16.1)	39	(26.5)	114	(19.5)	556	(18.9)
College graduate	41	(14.1)	279	(20.1)	94	(17.6)	25	(17.0)	76	(13.0)	515	(17.5)
Graduate school	44	(15.2)	256	(18.4)	88	(16.4)	20	(13.6)	90	(15.4)	498	(16.9)

	Watchful waiting (n = 348)		Radical prostatectomy (n = 1588)		External-beam radiotherapy (n = 626)		Brachytherapy (n = 175)		PADT* (n = 702)		Overall (n = 3439)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Income†												
$10,000 or less	32	(12.6)	69	(5.7)	51	(11.1)	15	(11.5)	72	(14.3)	239	(9.3)
$10,001–30,000	98	(38.7)	321	(26.5)	169	(36.7)	59	(45.4)	201	(39.8)	848	(33.1)
$30,001–50,000	65	(25.7)	342	(28.2)	119	(25.9)	35	(26.9)	116	(23.0)	677	(26.4)
$50,001–75,000	33	(13.0)	249	(20.5)	43	(9.3	9	(6.9)	60	(11.9)	394	(15.4)
More than $75,000	25	(9.9)	232	(19.1)	78	(17.0)	12	(9.2)	56	(11.1)	403	(15.7)

*PSA = prostate-specific antigen, PADT = primary androgen deprivation therapy.

†For income and education, percentages are based only on those patients with this data recorded.

Table 2

Frequency of neoadjuvant hormonal therapy use

		Frequency by year of diagnosis,* % of patients receiving neoadjuvant androgen ablation before treatment			
Primary treatment	Risk	1989–1992	1993–1995	1996–1998	1999–2001
Radical Prostatectomy	Overall	2.9	6.2	5.7	7.8
	Low	1.3	2.5	1.8	6.6
	Intermediate	2.0	7.2	5.7	7.5
	High	7.5	12.7	15.9	16.7
External-beam Radiotherapy	Overall	9.8	26.4	45.6	74.6
	Low	5.4	16.5	33.3	57.1
	Intermediate	4.9	17.6	42.2	73.5
	High	15.3	40.4	56.8	89.5
Brachytherapy	Overall	7.4	22.6	50.0	24.6
	Low	0.0	10.5	33.3	23.7
	Intermediate	0.0	30.4	42.9	28.6
	High	22.2	27.3	87.5	0.0

*For each primary local treatment (radical prostatectomy, external-beam radiotherapy, and brachytherapy), the percentage of men receiving neoadjuvant androgen ablation before treatment are presented for each time period. Trends are presented first for all patients in each treatment group and then by risk group.

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Table 3

Demographic and clinical factors associated with hormonal treatment

	Primary androgen deprivation*†			Neoadjuvant androgen deprivation*‡		
Factor	**%**	**Univariate OR (CI)**	**Multivariable OR (CI)**	**%**	**Univariate OR (CI)**	**Multivariable OR (CI)**
Year of diagnosis						
1989–1992 (ref)	16.3	1.0 (referent)	1.0 (referent)	3.9	1.0 (referent)	1.0 (referent)
1993–1995	18.7	1.2 (0.9 to 1.5)	1.6 (1.2 to 2.2)	8.5	2.5 (1.7 to 3.8)	3.0 (1.9 to 4.9)
1996–1998	28.1	2.0 (1.6 to 2.6)	3.2 (2.2 to 4.5)	12.4	4.3 (2.8 to 6.6)	5.8 (3.4 to 9.9)
1999–2001	22.4	1.5 (1.1 to 2.0)	2.8 (1.9 to 4.2)	17.4	5.8 (3.8 to 9.1)	9.8 (5.7 to 16.7)
		P<.001	*P*<.001		*P*<.001	*P*<.001
Risk						
Low (ref)	9.4	1.0 (referent)	1.0 (referent)	7.7	1.0 (referent)	1.0 (referent)
Intermediate	14.0	1.5 (1.2 to 1.9)	1.6 (1.1 to 2.1)	12.9	1.8 (1.3 to 2.5)	1.7 (1.2 to 2.5)
High	39.2	6.1 (4.9 to 7.7)	6.0 (4.5 to 8.0)	24.7	4.5 (3.2 to 6.2)	4.6 (3.1 to 6.8)
		P<.001	*P*<.001		*P*<.001	*P*<.001
Age						
<60 y (ref)	11.8	1.0 (referent)	1.0 (referent)	8.3	1.0 (referent)	1.0 (referent)
60–69 y	11.3	1.2 (0.9 to 1.6)	0.8 (0.6 to 1.2)	11.1	1.4 (1.0 to 2.0)	1.4 (0.9 to 2.3)
70–79 y	26.6	3.0 (2.3 to 4.0)	2.0 (1.4 to 2.9)	20.7	3.0 (2.1 to 4.4)	2.9 (1.8 to 4.5)
≥ 80 y	57.7	11.4 (7.8 to 16.6)	5.9 (3.6 to 8.5)	22.9	3.0 (1.3 to 6.6)	3.1 (1.2 to 8.1)
		P<.001	*P*<.001		*P*<.001	*P*<.001
Ethnicity						
Caucasian (ref)	19.6	1.0 (referent)		13.1	1.0 (referent)	
African-American	19.9	1.2 (0.9 to 1.5)		19.2	1.4 (1.0 to 2.0)	
Latino	20.8	1.1 (0.6 to 2.0)		8.6	1.0 (0.4 to 2.5)	
Other	23.3	1.8 (1.0 to 3.0)		14.3	1.3 (0.5 to 3.1)	
		P = .123	n/a		*P* = .261	n/a

	Primary androgen deprivation*†			Neoadjuvant androgen deprivation*‡		
Factor	**%**	**Univariate OR (CI)**	**Multivariable OR (CI)**	**%**	**Univariate OR (CI)**	**Multivariable OR (CI)**
Site type						
Community (ref)	19.8	1.0 (referent)		11.9	1.0 (referent)	1.0 (referent)
Academic	19.0	0.9 (0.7 to 1.2)		29.9	2.9 (2.1 to 4.0)	3.5 (2.2 to 5.4)
		P = .567	n/a		*P*<.001	*P*<.001
Location						
West (ref)	25.5	1.0 (referent)	1.0 (referent)	18.3	1.0 (referent)	
East	14.3	0.5 (0.4 to 0.6)	0.4 (0.3 to 0.5)	11.8	0.6 (0.4 to 0.8)	
Midwest	18.5	0.6 (0.4 to 0.8)	0.5 (0.3 to 0.7)	19.9	1.1 (0.7 to 1.6)	
South	25.8	1.0 (0.8 to 1.2)	0.8 (0.6 to 1.2)	11.4	0.7 (0.5 to 1.0)	
		P<.001	*P*<.001		*P*<.001	*P* = .723
Type of insurance						
Medicare alone (ref)	21.5	1.0 (referent)		19.9	1.0 (referent)	1.0 (referent)
Medicare/supp	19.5	0.8 (0.7 to 1.0)		12.0	0.5 (0.4 to 0.7)	0.8 (0.6 to 1.2)
Veterans Affairs	22.2	0.5 (0.3 to 0.9)		6.3	0.2 (0.1 to 0.9)	0.1 (0.0 to 0.5)
Other	13.4	1.1 (0.6 to 2.0)		18.7	1.0 (0.6 to 1.7)	0.6 (0.3 to 1.3)
		P = .098	*P* = .133		*P*<.001	*P* = .022
Level of education						
Grade school or less (ref)	26.6	1.0 (referent)		17.5	1.0 (referent)	
Some high school	22.3	0.8 (0.6 to 1.2)		13.7	0.6 (0.4 to 1.1)	
High school	20.0	0.7 (0.5 to 0.9)		14.9	0.6 (0.4 to 1.1)	
Some college	20.5	0.7 (0.5 to 1.0)		14.0	0.8 (0.5 to 1.3)	
College graduate	15.2	0.5 (0.3 to 0.7)		11.7	0.8 (0.5 to 1.3)	
Graduate school	18.1	0.6 (0.4 to 0.9)		11.9	0.7 (0.4 to 1.3)	
		P<.001	*P* = .504		*P* = .086	*P* = .680
Level of income						

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	Primary androgen deprivation*†			Neoadjuvant androgen deprivation*‡		
Factor	**%**	**Univariate OR (CI)**	**Multivariable OR (CI)**	**%**	**Univariate OR (CI)**	**Multivariable OR (CI)**
$10,000 or less (ref)	30.0	1.0 (referent)	1.0 (referent)	26.1	1.0 (referent)	
$10,001–30,000	23.7	0.7 (0.5 to 1.0)	0.8 (0.6 to 1.2)	14.8	0.5 (0.3 to 0.8)	
$30,001–50,000	17.1	0.5 (0.3 to 0.7)	0.6 (0.4 to 1.0)	13.9	0.5 (0.3 to 0.7)	
$50,001–75,000	15.2	0.4 (0.3 to 0.6)	0.6 (0.4 to 0.9)	8.3	0.3 (0.1 to 0.5)	
More than $75,000	13.9	0.4 (0.2 to 0.6)	0.5 (0.3 to 0.8)	10.9	0.3 (0.2 to 0.6)	
		$P<.001$	$P = .022$		$P<.001$	$P = .062$

*Univariate and multivariable odds ratios (OR) and 95% confidence intervals (95% CI) are presented for each factor associated with hormonal treatment. The referent levels are indicated for each factor; *P* values were determined from the χ^2 or Mantel-Haenszel χ^2 for univariate tests and from the Wald χ^2 for multivariable tests. Multivariable OR were not calculated for variables removed from the logistic regression model. All statistical tests were two-sided.

†Percentage of patients in each sociodemographic group who received primary androgen deprivation therapy.

‡Percentage of all patients in each group undergoing definitive local treatment (radical prostatectomy, external-beam radiotherapy, or brachytherapy) who received neoadjuvant androgen deprivation therapy.