Title

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Journal

Investigative Urology, 171(4)

ISSN

0021-0005

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Publication Date

2004-04-01

DOI

10.1097/01.ju.0000107247.81471.06

Peer reviewed

0022-5347/04/1714-1393/0
THE JOURNAL OF UROLOGY®

Vol. 171, 1393–1401, April 2004
Printed in U.S.A.
DOI: 10.1097/01.ju.0000107247.81471.06

Review Article

THE CONTEMPORARY MANAGEMENT OF PROSTATE CANCER IN THE UNITED STATES: LESSONS FROM THE CANCER OF THE PROSTATE STRATEGIC UROLOGIC RESEARCH ENDEAVOR (CAPSURE), A NATIONAL DISEASE REGISTRY

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ABSTRACT

Purpose: The epidemiology and treatment of prostate cancer have changed dramatically in the prostate specific antigen era. A large disease registry facilitates the longitudinal observation of trends in disease presentation, management and outcomes.

Materials and Methods: The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) is a national disease registry of more than 10,000 men with prostate cancer accrued at 31 primarily community based sites across the United States. Demographic, clinical, quality of life and resource use variables are collected on each patient. We reviewed key findings from the data base in the last 8 years in the areas of disease management trends, and oncological and quality of life outcomes.

Results: Prostate cancer is increasingly diagnosed with low risk clinical characteristics. With time patients have become less likely to receive pretreatment imaging tests, less likely to pursue watchful waiting and more likely to receive brachytherapy or hormonal therapy. Relatively few patients treated with radical prostatectomy in the database are under graded or under staged before surgery, whereas the surgical margin rate is comparable to that in academic series. CaPSURE data confirm the usefulness of percent positive biopsies in risk assessment and they have further been used to validate multiple preoperative nomograms. CaPSURE results strongly affirm the necessity of patient reported quality of life assessment. Multiple studies have compared the quality of life impact of various treatment options, particularly in terms of urinary and sexual function, and bother.

Conclusions: The presentation and management of prostate cancer have changed substantially in the last decade. CaPSURE will continue to track these trends as well as oncological and quality of life outcomes, and will continue to be an invaluable resource for the study of prostate cancer at the national level.

KEY WORDS: prostate; prostatic neoplasms; disease management; quality of life; databases, factual

Carcinoma of the prostate, the most common noncutaneous human malignancy, was estimated to have an incidence of 220,900 cases in 2003, accounting for approximately a third of new cancer diagnoses in men. In 2003, 28,900 prostate cancer deaths were expected, a mortality burden surpassed only by that of lung cancer.[1] With the advent of widespread prostate specific antigen (PSA) screening the initial detection of prevalent cases produced a steep increase in prostate cancer diagnoses, peaking in 1992 and followed by a sharp decrease. Since 1998, the annual incidence has been increasing again, whereas mortality has been decreasing steadily from a peak in 1994.[1] Early detection of cases has produced downward stage migration at presentation.[2,3] Earlier diagnosis and therapeutic advances have facilitated the increased use of aggressive local treatment, particularly radical prostatectomy (RP), external beam radiotherapy (EBRT) and more recently interstitial radiotherapy (brachytherapy).[3]

Evidence increasingly demonstrates a decrease in prostate cancer mortality with local treatment of low stage disease.[4] However, the natural history of the disease may be protracted, especially for screen detected tumors, and only 25% to 33% of men who are diagnosed with prostate cancer actually die of the tumors.[5,6] Moreover, all available treatments can negatively affect patient health related quality of life (HRQOL).[7] Indeed, given the excellent long-term survival after treatment for low risk tumors the literature on localized disease has in recent years focused

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more on minimizing the morbidity of therapy than on oncological outcomes.

Management practices for prostate cancer are changing constantly and are subject to myriad clinical, scientific, demographic and economic dynamics. Furthermore, practices may vary between academic and community settings, and among individual institutions. In an effort to document trends at a national level in disease management along with oncological and HRQOL outcomes the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) was founded in 1995 as a disease registry of men with all stages of prostate cancer. In this study we review our key findings in the last 8 years and discuss avenues for future research.

CaPSURE: STRUCTURE AND ORGANIZATION

A core group of 31 urological practice sites currently enroll patients in CaPSURE. Additional sites were active early in the project, such that 40 sites are represented in the database. These sites are primarily community based, although 4 are based at university centers and 3 are in Veterans Affairs (VA) medical centers, accounting for 4.8% and 3.2% of patients, respectively. At each practice site all men with biopsy proven prostate cancer are invited consecutively to join CaPSURE regardless of disease stage or treatment history.

CaPSURE collects approximately 1,000 clinical and patient reported variables. The clinical information, collected at baseline and each time the patient returns for care, includes history of prostate cancer diagnosis, biopsies, pathological findings, staging tests, primary and subsequent treatments (RP, EBRT, brachytherapy, primary androgen deprivation therapy [PADT], neoadjuvant androgen deprivation therapy [NADT], cryosurgery and watchful waiting [WW]), clinic procedures, Karnofsky performance status scores and medications. At each clinic visit the treating urologist completes a progress record, including current disease status, new prostate or unrelated diagnoses, disease signs and symptoms, and changes in medications. Imaging studies and laboratory tests are tracked and results are recorded when they are determined. Response choices for all variables are standardized.

In addition to the clinical data collected by the practicing physician, information is also collected from the patient. At enrollment each patient completes a questionnaire addressing sociodemographic parameters, comorbidities[8] and baseline HRQOL. Every 6 months thereafter patients are mailed a followup questionnaire. HRQOL components of the questionnaires include extensively validated survey instruments, namely the Medical Outcomes Study Short Form-36 (SF-36)[9] for general HRQOL and the University of California-Los Angeles Prostate Cancer Index (PCI)[10] for disease specific HRQOL. Since 1999, the questionnaires have also included a survey on patient satisfaction with care[11,12] and an assessment of fear of cancer recurrence.[13]

Other sections of the patient questionnaires assess the use of all health services in the prior 6 months, including emergency department visits, outpatient procedures, radiology and diagnostic tests, physical and occupational therapy, physician consultations, medications, nontraditional therapies and hospitalizations. All patient reported hospitalizations and emergency department use are verified with patient permission via a review of hospital discharge summaries, and length of stay, discharge status, discharge diagnosis and procedures performed are recorded. The response rate to the questionnaires is approximately 75% at each mailing.

Data on patients diagnosed prior to 1995 but still followed by a urologist were initially entered retrospectively. For those diagnosed since 1995, all data have been prospectively collected. Informed consent is obtained from each patient under local institutional review board supervision. Patients are treated according to their physician usual practices and they are followed until death or study withdrawal. Mortality information is requested from the Bureau of Vital Statistics or National Death Index to verify the exact date, primary causes and location of death.

To facilitate data collection the CaPSURE web based, relational data base enables personnel at urology practice sites to enter clinical data remotely. Security and integrity of data are ensured through the use of passwords with automatic time out, 128 bit encryption technology for electronic transfer of data and complete daily backup. This web based system allows continuous real-time access to data for the evaluation of site specific and national data, and for research purposes. Completeness and accuracy of the data are ensured by random sample chart review at periodic intervals. Questionnaires, hospital audits, death certificates and surgical pathology reports are entered using optical character recognition scanning software, which has demonstrated higher accuracy compared with manual data entry. Additional details of the project methodology, including quality assurance, have been reported previously.[14]

CAPSURE: PATIENT CHARACTERISTICS

Table 1 lists the sociodemographic characteristics of the patients enrolled in CaPSURE. Median age at diagnosis is 67 years and almost 75% of the men are between ages 60 and 79 years. The majority of participants are white with about 10% black representation and few participants of other ethnicities. There is fairly even distribution across socioeconomic strata, as assessed via education and income level. More than half of CaPSURE patients are covered by

TABLE 1. *Sociodemographic characteristics of CaPSURE participants*

	No. (%)	
Age at diagnosis:		
Less than 40	4	(0.0)
40–49	225	(2.3)
50–59	1,901	(19.0)
60–69	4,109	(41.0)
70–79	3,246	(32.4)
80 or Greater	533	(5.3)
Ethnicity:		
Black	1,007	(10.1)
White	8,652	(86.4)
Other	291	(2.9)
Unknown	68	(0.7)
Education:		
Grade school	1,392	(13.9)
High school graduate	2,018	(20.1)
Some college	1,528	(15.3)
College graduate	1,302	(13.0)
Graduate school	1,454	(14.5)
Unknown	2,324	(23.2)
Annual income ($):		
Less than 30,000	2,546	(25.4)
30,001–50,000	1,691	(16.9)
50,001–75,000	1,121	(11.2)
Greater than 75,000	1,375	(13.7)
Unknown	3,285	(32.8)
Insurance:		
Medicare only	4,095	(40.9)
Medicare plus supplemental	1,235	(12.3)
Preferred provider organization only	1,342	(13.4)
Health maintenance organization only	1,810	(18.1)
Fee for service	678	(6.8)
Other/unknown	858	(8.6)
Region:		
West	1,530	(15.3)
Midwest	1,681	(16.8)
South	3,533	(35.3)
Northeast	3,274	(32.7)
Site type:		
Academic	491	(4.9)
Community	9,204	(91.9)
VA	323	(3.2)
Total	10,018	(100.0)

Medicare with or without supplemental policies and the remainder have various health coverage types. Two-thirds of the patients are treated at urological practices located in the south or northeast and more than 90% are seen at community based practices.

Table 2 lists CaPSURE participant clinical characteristics. Of those with known comorbidity data half have zero or 1 comorbid illness (median 1). Median PSA at diagnosis is 7.3 ng/ml. More than two-thirds of patients with a known PSA at diagnosis present with a PSA of 10 ng/ml or less. A majority present with a biopsy Gleason score of 5 or 6 and with clinical stage T1 or T2 disease. In the overall database patients are distributed fairly evenly among low, intermediate and high risk groups, as defined by D'Amico et al,[15] although with time the proportion with low risk disease has been increasing and that with high risk disease has been decreasing. RP is the most common primary treatment, followed sequentially by PADT, EBRT, brachytherapy, WW and cryotherapy.

A study of 241 CaPSURE patients enrolled at VA medical centers showed that they are much more likely than the general patient population to be black, and have lower income, less education and more comorbidity at presentation. They also have significantly higher risk disease in terms of PSA at diagnosis and biopsy Gleason score. They are more likely to undergo WW or receive PADT and less likely to receive definitive local therapy.[16]

Temporal trends in disease presentation. We recently examined changes with time in patient risk characteristics at diagnosis. Patients presenting with low risk disease, that is, PSA 10 ng/ml or less, Gleason score under 7 with no pattern 4 or 5 disease on biopsy and clinical stage T1c or T2a,[15] have increased from 31% in 1989 to 1990, to 47% in 2001 to 2002. During the same time those with high risk disease, that is PSA greater than 20 ng/ml, Gleason 8 to 10 biopsy or stage T3 to 4,[15] decreased from 41% to 15%. T1 tumors became increasingly prevalent, as did those with Gleason 7 biopsies and those associated with PSA 4 to 10 ng/ml. In the early years of the study patients were most likely to be classified as at high risk due to high PSA, whereas more recently high risk patients were more likely to have low PSA and a high Gleason score.[17] It has previously been shown that Gleason scores have been increasing in the last decade as a result of changes in pathological grading practices,[18] suggesting that even as patients are being diagnosed with high risk disease less commonly, a contemporary patient considered to be at high risk may have a better prognosis than an earlier patient at high risk. Subgroup analysis of black patients in CaPSURE showed they had consistently higher risk characteristics but trends toward better risk at presentation were identical to those in the general data base.[17]

TABLE 2. *Clinical characteristics of CaPSURE participants*

	No. (%)
Comorbidity:	
None	1,811 (18.1)
1	2,195 (21.9)
2	1,898 (19.0)
3	1,199 (12.0)
4 or More	872 (8.7)
Unknown	2,043 (20.4)
PSA at diagnosis (ng/ml):	
4 or Less	1,102 (11.0)
4.1–10	4,868 (48.6)
10.1–20	1,608 (16.1)
Greater than 20	1,217 (12.2)
Unknown	1,223 (12.2)
Gleason score:	
2–4	812 (8.1)
5–6	5,207 (52.0)
7	2,114 (21.1)
8–10	934 (9.3)
Unknown	951 (9.5)
Clinical stage:	
T1	3,498 (34.9)
T2	5,046 (50.4)
T3	551 (5.5)
T4	48 (0.5)
Unknown	875 (8.7)
Risk group:	
Low	2,974 (29.7)
Intermediate	3,247 (32.4)
High	2,614 (26.1)
Unknown	1,183 (11.8)
Primary treatment:	
RP	4,128 (41.2)
Cryotherapy	281 (2.8)
Brachytherapy	1,013 (10.1)
EBRT	1,206 (12.0)
PADT	1,693 (16.9)
WW	604 (6.0)
Unknown	1,093 (10.9)
Total	10,018 (100.0)

Comorbidity is defined by the Charlson index[8] and risk group is defined by the D'Amico classification.[15]

NATIONAL PRACTICE PATTERNS

The majority of CaPSURE patients were diagnosed during the PSA era and treated in community based settings. Participating physicians treat according to their usual practices following no specified protocols or pathways. Patients remain eligible for other clinical trials and treatments associated with any such trials are reported as they are received. Several caveats should be noted. Data on patients accessioned prior to June 1, 1995 were entered retrospectively and, thus, they may be vulnerable to reporting bias. However, at least 1 prior analysis showed no difference in resource use between patients diagnosed before this date and those diagnosed between June 1995 and June 1997.[19]

While CaPSURE represents a mix of locales and practice types, the sites were not chosen at random and, thus, they cannot be assumed to represent a statistically valid sample of United States practice patterns. For example, white patients are relatively over represented in CaPSURE compared with national census data. Finally, only diagnostic and therapeutic interventions ordered or coordinated by participating urologists are recorded. Patient reports of resource use and review of hospital records, as described, help minimize this potential treatment bias. Despite these cautionary notes we believe that our data provide the best available description of national practice patterns and they have provided the basis for a number of interesting descriptive studies.

Staging tests. Imaging studies performed in men diagnosed with prostate cancer serve to facilitate optimal treatment planning. However, staging investigations are associated with low but definite risks and with significant costs to the health care system. Analyses dating back to the early 1990s demonstrated a minimal benefit for imaging tests in patients with low risk disease characteristics.[20]

Kindrick et al first analyzed the use of imaging tests in CaPSURE among patients diagnosed between 1989 and 1997, finding widespread and consistent overuse with no significant changes with time even as the patient disease burden at diagnosis decreased throughout the 1990s.[19] However, followup analysis reporting data through 2001 showed that rates of bone scan and computerized tomography use decreased dramatically in recent years with the greatest decreases in patients at lower risk. Indeed, whereas among early CaPSURE patients disease risk exerted no influence on the likelihood of imaging, in more recent years rates of imaging are strongly associated with risk, as defined earlier by T stage, PSA and Gleason score.[21]

Primary treatment. Given the prolonged natural history of localized prostate cancer and the HRQOL impact of all available active treatments, increased attention has been given recently to WW as a viable alternative for the initial management of prostate tumors with favorable risk characteristics. A recent European randomized trial of WW vs RP found

higher rates of metastases and disease specific mortality among patients treated with WW vs RP but study patients were diagnosed prior to the PSA era and had tumors that would generally not be considered low risk by contemporary standards.[4] Indeed, recently reported cohort studies showed favorable early outcomes for WW in carefully selected patients.[22,23]

An early cross-sectional analysis from CaPSURE showed that only 8.2% of patients in the database pursued WW as primary management.[24] We hypothesized that given the growing interest in WW and the trend discussed toward more patients being diagnosed with low risk disease we would see increasing use of WW with time in patients at low risk in CaPSURE. However, WW use in fact decreased from 9.5% in 1992 to 1994, to 5.5% in 1998 to 2000 with the sharpest decreases in low risk cases.[25]

We subsequently looked in greater detail at treatment trends in patients at low risk and found that since the start of the PSA era, the use of WW in those at low risk has decreased by more than half from 20% in 1993 to 1995, to 8% in 1999 to 2001. During the same time the use of EBRT decreased from 13% to 7%, while that of RP decreased slightly from 55% to 52%. In contrast, the use of PADT and brachytherapy increased significantly from 7% to 12% and 4% to 22%, respectively. Even in patients 75 years old or older WW use decreased from 52% to 24%, while PADT increased from 23% to 30% and brachytherapy increased from 3% to 31%.[26]

In the cross-sectional study more than half of patients on WW underwent secondary treatment within 5 years, especially those who were younger or had higher PSA at diagnosis.[24] Most of them received androgen deprivation therapy. Another recent study identified predictors of eventual treatment in patients on WW, showing that PSA kinetics were a strong driver of treatment decisions.[25] Patients with a PSA increase of greater than 5 ng/ml were almost 4 times as likely to elect treatment as those with an increase of less than 2 ng/ml. High risk baseline characteristics were also significant predictors of eventual active treatment.

We have also analyzed in-depth practice patterns in the use of androgen ablation therapy for localized prostate cancer. The use of PADT as monotherapy has increased dramatically across groups in the last decade from 5% to 14%, 9% to 20% and 33% to 48% in low, intermediate and high risk cases, respectively, from 1989 to 1990, to 2000 to 2001. Likewise, NADT use has increased from 3% to 8% of patients undergoing RP, 10% to 75% of those receiving EBRT and 7% to 25% of those receiving brachytherapy.[27] The explanations for these trends in primary management strategies are certainly multifactorial, encompassing a number of patient and physician driven clinical, psychological, medicolegal and economic factors. The extent to which they respond to developments in the literature and to continuing changes in the health care system will provide a fascinating avenue for continued research.

Costs. Finally, resource use data in CaPSURE offer a means of studying healthcare system wide cost implications of various management strategies for prostate cancer. Penson et al analyzed stage adjusted, first year costs associated with various treatment options based on Medicare payment schedules.[28] They found that the mean cost of prostate cancer treatment in the first year after diagnosis was $6,375 with a trend toward significantly higher costs for higher stage disease. Costs were not different between patients with RP and EBRT but they were significantly higher for patients receiving NADT before either primary treatment.

ONCOLOGICAL NATIONAL OUTCOMES

Under staging and under grading. Preoperative clinical assessment of prostate cancer extent and aggressiveness by definition risks an underestimation of disease risk due to sampling error. Rectal examination detects only peripheral zone tumors and it is marked by significant interobserver variability. Even extended pattern mapped biopsies may not yield a representative sample of the tumor. Grossfeld et al compared clinical staging information and biopsy Gleason grades from 1313 patients in CaPSURE treated with RP to stage and grade as determined from the prostatectomy specimens.[29] They found under staging (that is clinically localized, pathological stages T3 to 4 or N+) in 24% of patients and clinically significant (that is biopsy patterns 1 to 3 and pathological patterns 4 to 5) under grading in 30% of specimens. PSA at diagnosis, biopsy Gleason score and percent positive biopsies predicted under staging. Prior studies from large, single institution series showed that the incidence of under staging was 36% to 60%.[30–32] Likewise, under grading has previously been noted in 43% of cases.[33] The lower incidence of under graded and extraprostatic disease found in CaPSURE likely reflects the downward risk migration discussed as well as improvements in biopsy techniques with more tumors in the PSA era detected at early stage and low grade.

Positive surgical margins. The incidence of positive surgical margins following RP is 14% to 46% in published series[34] and in most studies the finding of positive margins has been found to predict adverse clinical outcomes.[35–37] The external validity of this finding in the community setting was assessed by reviewing the pathology reports of 1,383 patients in CaPSURE. Of these patients 465 (34%) had positive surgical margins, a rate consistent with that in academic analyses. After controlling for sociodemographic and clinical characteristics patients with positive surgical margins were approximately 1.9 times as likely to receive secondary treatment than those with negative margins ($p = 0.0011$) and 2.6 times as likely to experience PSA recurrence after RP ($p = 0.06$). The location and number of positive margins had little effect on the outcomes measured.[38]

Outcome prediction. Percent Positive Biopsies: Increasing evidence suggests that information derived from the results of the diagnostic biopsy contributes significantly to accurate risk assessment in patients with newly diagnosed localized disease.[39–41] The prognostic value of the percent of positive biopsies cores was recently validated using CaPSURE data. Of 1,265 patients treated with RP 320 (25%) had recurrence at a median of 3.3 years following surgery. PSA at diagnosis, biopsy Gleason score, percent positive biopsies and black ethnicity were significant independent predictors of disease recurrence. Moreover, percent positive biopsies was a significant predictor of disease recurrence in each of the low, intermediate and high risk groups, confirming that it may be a useful variable to identify patients with adverse risk features who may be appropriate candidates for aggressive local therapy or who may benefit from adjuvant treatment. Also significant is the confirmation that biopsy data obtained in the community and assessed by diverse pathologists offers consistent prognostic information.[42]

Nomogram Validation Studies: CaPSURE has proved to be an excellent tool with which to test the external validity of nomograms developed in academic, frequently single center patient series. External validation is a crucial step in nomogram development and the availability of a large, community based cohort provides an excellent means of assessing the real world applicability of university based instruments. The Partin tables, which predict pathological outcomes after prostatectomy using preoperative PSA, Gleason score and clinical stage, were developed and validated in patients from 3 academic institutions and they are widely used in academic and community settings.[43,44] The performance of these tables in the community setting was assessed among 1,162 patients in CaPSURE undergoing RP. ROCs were 0.684 for predicting organ confined disease, 0.614 for capsular pene-

tration, 0.726 for seminal vesicle involvement and 0.766 for lymph node involvement. While these values indicate good performance for predicting seminal vesicle and lymph node involvement, they are lower than those reported in the original academic series, perhaps due to differences in case mix in terms of baseline risk in the community setting.[45]

Pathological outcomes do not always correlate with clinical outcomes in terms of recurrence and progression. Therefore, CaPSURE data have also been used to validate risk assessment instruments based on the probability of biochemical recurrence or second treatment. For example, a model developed by Bauer et al stratifies patients into low (72% 7-year disease-free survival [DFS]), intermediate (42% DFS) or high (28% DFS) risk of recurrence based on preoperative PSA, pathological stage, postoperative Gleason sum and ethnicity.[46] This model was validated and refined using data combined from CaPSURE and the Department of Defense Center for Prostatic Disease Research (CPDR) database. Because the validation study included a much larger cohort (1,515 patients, including 1,012 from CaPSURE and 503 from CPDR), stratification could be improved using the same variables to 4 levels with very low (85% DFS), low (66% DFS), high (51% DFS) and very high (21% DFS) risk of recurrence.[47]

More recently we performed a similar validation study using CaPSURE cases only on a nomogram developed by Kattan et al which predicts 5-year DFS based only on preoperative parameters, namely PSA at diagnosis, Gleason score and clinical T stage.[48] Like the Partin tables, the Kattan nomogram was developed in an academic setting and it has subsequently been validated in a cohort drawn from multiple academic institutions.[49] We analyzed the performance of the nomogram in 1,701 patients in CaPSURE treated with RP, of whom 24% experienced biochemical recurrence or received second treatment. The overall concordance index for nomogram predicted survival in regard to actuarial 5-year survival was 0.68, somewhat lower than the predictive power calculated from the academic validation cohort. In particular, the Kattan nomogram overestimates survival in community patients with high scores, that is those at relatively low risk for recurrence.[50] We are currently working to refine this nomogram to achieve better predictive power in the community setting.

CaPSURE data have also been used in conjunction with single institution data from University of California-San Francisco to examine prognostic factors in patients at high risk undergoing surgery. In those with PSA greater than 20 ng/ml, Gleason score 8 or greater and/or stage T2c or higher PSA, Gleason score and percent positive biopsies independently predicted recurrence at 3 years, while stage and age did not.[51] Another recent study from CaPSURE examined the impact of ethnicity on biochemical recurrence after RP and showed the greatest difference in outcomes between black and white patients with high risk characteristics.[52] Five-year biochemical DFS rates were estimated to be 65% in white and 28% in black patients. However, on multivariate analysis controlling for income and education (variables closely associated with ethnicity) ethnicity was no longer an independent predictor of outcome.[52]

PSA doubling time. Clinical research in prostate cancer is complicated by a natural history that is highly protracted relative to most other tumors. Even in a patient who will ultimately die of prostate cancer years may pass at each stage of progression, namely PSA recurrence, the emergence of androgen independent disease, clinical metastasis and death. Improvement or delay in cause specific mortality is the gold standard outcome targeted by most clinical trials and mandated by the Food and Drug Administration for new drug development but achieving this outcome may require a trial spanning a decade or more. As typically defined, biochemical recurrence (any PSA above a low threshold, typically 0.2 ng/ml, for patients after RP or 3 consecutive increases after a nadir for patients who receive radiation) is unsatisfactory because such definitions do not reliably predict ultimate cause specific mortality and do not allow comparisons between patients treated with surgery and those treated with radiation.

Again in conjunction with the CPDR data base CaPSURE has formed the basis of a landmark study to establish PSA doubling time (PSADT) as a surrogate outcome for prostate cancer clinical trials. D'Amico et al analyzed posttreatment PSA kinetics in 5,918 and 2,751 patients treated with RP and EBRT, respectively, in the 2 databases between 1988 and 2002.[53] A PSADT of less than 3 months following treatment and biochemical recurrence was a powerful predictor not only of cause specific mortality ($p < 0.0001$), but also of overall mortality ($p < 0.0001$). Moreover, given PSADT less than 3 months as a surrogate outcome, primary treatment (RP or EBRT) did not significantly predict cause specific ($p = 0.37$) or overall ($p = 0.74$) mortality. These findings, which were possible only with the number of patients and extended followup present in large disease registries, suggest that PSADT may function as a valid short-term end point for future studies of prostate cancer therapy.

QUALITY OF LIFE NATIONAL OUTCOMES

Even in the absence of treatment the extended natural history of localized prostate cancer[54] mandates the highest possible standard of care in terms of the preservation of HRQOL. It is essential even more so than in other areas of oncology that treatments aimed at prolonging life exert a minimal detrimental impact on quality of life because any such negative impact may be experienced by patients for an extended time. CaPSURE has proved to be an invaluable resource for the prospective, longitudinal assessment of patient reported HRQOL outcomes and it has successfully addressed a number of questions in this area of prostate cancer research.[55]

The importance of patient reported outcomes. Previous groups have argued that HRQOL outcomes should be reported directly by patients rather than assessed by physicians and they have found underestimation by physicians of the HRQOL impact of treatment in the context of metastatic prostate cancer.[56] CaPSURE HRQOL data reported by a large number of physicians and patients have proved to be an ideal means of evaluating differences between patient and physician reported HROQL outcomes. In one of the first CaPSURE outcomes studies Litwin et al compared patient responses on the SF-36 and PCI to symptoms recorded by urologists for 2,252 patients with prostate cancer who were 42 to 95 years old.[57] They found that physician assessments were not well associated with patient reported outcomes, significantly underestimating HRQOL impairment in such domains as overall physician function, fatigue, bone pain, urinary function and sexual function. Physician underestimation of HROQL impact was of greater magnitude for the general health domains than for the disease specific domains.

A more recent CaPSURE study focused specifically on the question of erectile function following treatment.[58] Reported potency rates after EBRT and RP have varied widely from 2% to 86% of men following RT[59–62] and 14% to 82% following RP.[31,63,64] This variance may be attributable to the limitations of physician reported outcome assessment, differences in patient populations, variation in time points relative to treatment at which potency is evaluated and the multiplicity of potency definitions used in contemporary studies.[65]

We analyzed scores on the sexual function and bother domains of the PCI, comparing men who would be classified as potent or impotent based on the objective criterion of erections greater than 50% of the time when desired, and/or vaginal or anal intercourse at least 1 time in the prior 4

weeks, a definition best approximating the National Institutes of Health Consensus definition of impotence.[66] We found that of 5,135 men completing at least 1 questionnaire following treatment and not using erectile aids 27% met the criterion definition of potency. While there were significant differences between potent and impotent men in terms of sexual function and sexual bother, there was also broad overlap between the 2 groups in the 2 HRQOL domains, confirming a multidimensional picture of sexual HRQOL that is under appreciated by simple assessment of potency.[58]

Effect of treatment on HRQOL. Many studies to date that evaluated HRQOL after treatment in prostate cancer are cross-sectional or retrospective in nature.[67,68] These studies showed little impact on general measures of HRQOL but indicated differences in treatment groups in disease specific domains, such as urinary, bowel or sexual function. Because CaPSURE collects HRQOL data directly from patients at baseline and during followup, it provides an ideal data set for studying longitudinal effects of various treatments over time.

An early CaPSURE HRQOL study compared outcomes in RP, EBRT, WW and PADT cases for the first 2 years following treatment.[68] Of 692 evaluable patients those undergoing RP had low scores on the general and disease specific HRQOL instruments immediately postoperatively but they experienced dramatic increases in all domains by 1 year following surgery. In postoperative year 2 there were slight but significant decreases in the urinary and bowel domains of the PCI but improvement in the sexual domains. In patients treated with EBRT, WW and PADT scores were relatively stable across most domains except sexual function scores, which decreased in all treatment groups.[69]

Subsequent studies assessed individual HRQOL domains in greater detail. Litwin et al examined urinary function and bother in 564 newly diagnosed patients undergoing RP or EBRT.[70] Immediately following treatment urinary function was significantly worse in those treated with RP vs EBRT. However, by the end of postoperative year 1 the urinary function of patients with RP approached that of patients with EBRT and it remained stable during year 2. In contrast, urinary bother was worse following treatment in patients treated with EBRT vs RP following treatment. While patients who received EBRT improved during the study period, they continued to have significantly greater bother than those treated with RP by the end of year 2 following treatment. In interpreting the divergent urinary function and bother scores between the treatment groups it is important to stress that the urinary function domain in the PCI focuses on incontinence symptoms typically seen in patients with RP rather than the irritative symptoms that are of primary concern to patients with EBRT. In contrast, the bother domain does not distinguish among types of symptoms.

In another study Litwin et al assessed sexual function and bother in patients undergoing nerve sparing RP, nonnerve sparing RP and EBRT.[71] As in the urinary function study, sexual function was better in the EBRT group immediately after treatment, and the RP and EBRT groups showed improvement in year 1. In year 2 patients with RP continued to improve, while those with EBRT started to show a significant decrease. This decrease after EBRT was greatest in older patients, while following RP older patients approached their low baseline function by 2 years. Sexual function was significantly better in patients treated with RP who received nerve sparing and in those using erectile aids. Average sexual bother did not change significantly with time regardless of treatment. Results in the urinary and sexual function studies concur with and validate those previously reported in a single center cohort using less well validated HRQOL measures.[72]

Impact of ethnicity. As discussed, CaPSURE is one of few prostate cancer registries that includes a significant number of nonwhite patients. Despite the expanding literature on clinical differences among ethnic groups with prostate cancer, in particular the higher incidence and elevated risk of mortality in black patients, little is known about the effects of prostate cancer and its treatment on HRQOL in this group. Therefore, using CaPSURE data the baseline demographic, clinical and HRQOL characteristics of black vs white men were evaluated. Black patients in CaPSURE are younger than white patients and they have lower levels of income and education. They present with more advanced disease in terms of PSA at diagnosis and pathological stage.

In terms of HRQOL black men have lower scores on multiple domains of the SF-36 and PCI, including general health, physical function, role function emotional, self-esteem, health distress, prostate cancer interference, bowel function and sexual bother. On the other hand, they had higher sexual function scores, again emphasizing the independence of function and bother domains, and the importance of assessing each of them. Differences in scores were most pronounced in the generic HRQOL domains. There were also significant differences between black and white patients in terms of HRQOL changes with time with black patients generally faring worse than white patients.[73] These findings are consistent with another CaPSURE analysis showing that patients with low socioeconomic status had lower baseline scores on all SF-36 general HRQOL domains and on 4 of the 8 disease specific PCI domains.[74]

CONCLUSIONS

The CaPSURE transition to a web based interface facilitated additional practical applications for participating urologists, who may now benchmark their aggregate outcomes against the overall data base. In the future patients may be able to record their HRQOL and resource use directly through the web interface and compare their outcomes to those of similar patients. The CaPSURE registry project represents a highly successful and ongoing alliance between academia and industry. As more patients are enrolled and longer followup data are accumulated, CaPSURE data will only become more robust. The registry will continue to be a unique and invaluable resource for patients, physicians, researchers, health policymakers and industry leaders interested in tracking prostate cancer epidemiological trends, practice patterns, and oncological and HRQOL outcomes.

For more information on CaPSURE, including an up-to-date list of publications and abstracts deriving from the database, please refer to our website: <www.capsure.net>. The CaPSURE data base is managed by the Urology Outcomes Research Group, Department of Urology, University of California-San Francisco. It has been funded since its inception by a grant from TAP Pharmaceutical Products, Inc.

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