Follow-up Prostate Cancer Treatments After Radical Prostatectomy: a Population-Based Study

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Background: Radical prostatectomy is one of the most commonly used curative procedures for the treatment of localized prostate cancer. The probability that a patient will undergo additional cancer therapy after this procedure is largely unknown. Purpose: The objective was to determine the likelihood of additional cancer therapy after radical prostatectomy. Methods: Data for this study were derived from a linked dataset that combined information from the Surveillance, Epidemiology, and End Results Program and Medicare hospital and physician claims. Records were included in this study if patient histories met the following criteria: (a) residing in Connecticut, Washington (Seattle–Puget Sound), or Georgia (Metropolitan Atlanta); (b) having been diagnosed with prostate cancer during the period from January 1, 1985, through December 31, 1991; (c) undergoing radical prostatectomy by December 31, 1992; and (d) having no evidence of other types of cancer. Patients were considered to have had additional cancer therapy if they had had radiation therapy, orchietomy, and/or androgen-deprivation therapy by injection after radical prostatectomy. The interval between the initial treatment and any follow-up treatment was calculated from the date of radical prostatectomy to the 1st day of the follow-up cancer therapy. All presented probabilities are based on Kaplan–Meier estimates. Results: The study population consisted of 3494 Medicare patients, 3173 of whom underwent radical prostatectomy within 3 months of prostate cancer diagnosis. Although radical prostatectomy is often reserved for localized cancer, less than 60% (1934) of patients whose records were included in this study had organ-confined disease, according to final surgical pathology. Overall, the 5-year cumulative incidence of having any additional cancer treatment after radical prostatectomy reached 34.9% (95% confidence interval [CI] = 31.5%-38.5%). For patients with pathologically organ-confined cancer, the 5-year cumulative incidence was 24.3% (95% CI = 20.8%-29.3%) overall and ranged from 15.6% (95% CI = 9.7%-24.5%) for well-differentiated cancer (Gleason scores 2-4) to 41.5% (95% CI = 27.9%-58.4%) for poorly differentiated cancer (Gleason scores 8-10). The corresponding figures for pathologically regional cancer were 22.7% (95% CI = 12.0%-40.5%) and 68.1% (95% CI = 58.7%-77.1%). Conclusion: Further treatment of prostate cancer was done in about one third of patients who had had a radical prostatectomy with curative intent and in about one quarter of patients who were found to have organ-confined disease. Implications: Given the common requirement for follow-up cancer treatments after radical prostatectomy and the uncertainties about the effectiveness of the various follow-up treatment strategies, further investigation of these treatments is warranted. [J Natl Cancer Inst 1996;88:166-73]

The incidence of prostate cancer, the most common non-skin cancer among U.S. men, has risen dramatically during the past decade. It is estimated that 244 000 U.S. men will be diagnosed with this disease in 1995 (1). The majority of these newly diagnosed patients will have clinically localized tumors. Many clinicians advocate either radical prostatectomy or external-beam radiation therapy as potentially curative therapy for cancers confined to the prostate gland (2). Some physicians, however, have questioned the value of these treatments, especially for older patients with low-grade tumors (3-5). During the late 1980s, the rate of radical prostatectomy among Medicare recipients increased more than fivefold throughout the United States, but wide geographic variation in the use of this procedure...
dure suggests disagreements concerning its net benefits (6,7). In part, these disagreements reflect scientific uncertainty: clinical trials have not demonstrated whether or not active treatment improves life expectancy (8). Clinical trials of sufficient power to provide a definitive answer may not be available for years (9,10). In the meantime, patients and physicians must rely on nonexperimental evidence for decision-making such as can be provided by claims data and cancer registries to learn about the sequelae of alternative options.

Although some researchers (11-13) in selected academic medical centers report that cancer recurrence as determined by prostate-specific antigen (PSA) elevation is relatively uncommon after radical prostatectomy, it is not clear whether these results can be replicated in community practice. Furthermore, at the present time, little is known about clinical practice patterns concerning the use of follow-up cancer treatments after radical prostatectomy. The treatment of patients with detectable PSA but no detectable metastases after radical prostatectomy remains controversial (14); as a result, the probability of requiring additional cancer treatment after radical prostatectomy is largely unknown.

The goal of our study was to provide estimates on the likelihood of requiring additional cancer therapy after radical prostatectomy in several geographically defined populations.

Subjects and Methods

Sources of Data

Data were obtained from two sources: 1) the population-based cancer registries sponsored by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute and 2) the Medicare claims database. The SEER Program provides clinical information and data on each cancer at presentation and its initial treatment, whereas Medicare files provide data concerning patient demographics, health care resource consumption, and comorbidity status. By linking these two files for patients aged 65 years or older, a longitudinal profile of health care utilization can be constructed for prostate cancer patients with almost complete follow-up. SEER data could be linked with Medicare claims data for approximately 94% of prostate cancer cases diagnosed during the period from 1985 through 1991 by use of personal identifiers, such as Social Security number, first and last names, sex, date of birth, and date of death (15). Men aged 65 years or older account for approximately 82% of newly diagnosed prostate cancer cases, and 62% of all radical prostatectomies in this era were performed on men in this age group (16).

SEER Program data. The SEER Program consists of 10 population-based registries whose goal is to collect information on all cancer cases diagnosed in their defined geographic areas. Trained abstractors collect information from multiple sources, including hospital records, outpatient clinics, free-standing radiation centers, private laboratories, and doctors' offices. The following data elements are available in the SEER database: patient demographic characteristics, the date and location of cancer diagnosis, the extent and histology of the disease, the initial cancer-directed treatment, subsequent vital status over time, and cause of death. Patients are followed until death. To ensure accuracy, SEER uses standardized coding forms and employs rigorous quality-control procedures (17).

Medicare claims. The Medicare Program, administered by the Health Care Financing Administration (HCFA), provides health insurance to approximately 96% of all persons aged 65 years or older (18). Covered services include inpatient and outpatient hospital care, physician services, durable medical equipment, home health agency care, skilled nursing facilities, and hospice care. Self-administered prescription medications and long-term unskilled care are not covered. The claims file used for this study includes the following three Medicare files and a separate database developed by the Center for Health Economics Research, Waltham, MA (CHER):

Denominator files (1985-1992)—For each Medicare beneficiary, these files contain information on Medicare entitlement, health maintenance organization (HMO) enrollment status, age, race, ZIP code of residence, date of birth, and date of death.

Medicare Provider Analysis and Review (MEDPAR) (1985-1992) (19). MEDPAR files contain information on hospital inpatient stays for each Medicare beneficiary and include dates of hospital admissions and discharges, hospital identifiers, diagnosis codes (up to 5), procedure codes (up to 3), and diagnosis-related group codes. The diagnosis and procedure codes are based on the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) (20).

Part B National Claims History (NCH) (1991-1992)—Claims data covering services provided by physicians were obtained for 1991 and 1992 from Medicare's NCH file. Each record contains the date of service and the actual procedure or service performed. Procedures are coded on the basis of the Physicians' Current Procedural Terminology, 4th edition (CPT-4), of the American Medical Association (AMA) (20). This file contains more than 10,000 specific codes used to identify procedures billed by physicians.

CHER database (1985-1990)—Claims data for physician services during 1985-1990 were obtained from the CHER database, which was developed under contract to HCFA's Office of Research and Demonstrations. The CHER database consists of physician claims data for all Medicare beneficiaries collected directly from insurance carriers in 11 states, including three states that overlap the SEER areas used in this study: Connecticut, Georgia (Metropolitan Atlanta), and Washington (Seattle–Puget Sound). Similar to Medicare physician claims data, the CHER database contains dates of service and procedure codes based on the AMA's CPT-4 for each beneficiary. The CHER files have been edited to remove duplicate, reprocessed, and denied claims and to identify missing or erroneous data. In addition, all carrier or HCFA-assigned procedure codes were reclassified to the AMA's CPT-4 equivalent.

Sample Selection

We identified 8771 patients who were aged 65 years or older, diagnosed with prostate cancer during the period from January 1, 1985, through December 31, 1991, and who underwent radical prostatectomy by the end of 1992. Radical prostatectomy was defined as removal of the prostate, ejaculatory ducts, and seminal vesicles, with or without dissection of pelvic lymph nodes. A total of 1209 men who were HMO members or who did not have full Medicare coverage from the time of diagnosis through the follow-up period were excluded, since their longitudinal claims histories are likely to be incomplete. We restricted the study to the three SEER regions where physician claims data were available for all Medicare beneficiaries from the CHER database; as a result, 3152 patients were excluded. In addition, 916 men who had other types of cancer diagnosed before or after the diagnosis of prostate cancer were excluded to ensure that additional cancer treatment was administered only for the management of prostate cancer. These exclusions resulted in a final sample of 3494 cases from the three geographic areas. The majority of these patients (3173) underwent radical prostatectomy within 3 months of prostate cancer diagnosis. Only eight patients had hormone therapy before radical prostatectomy.

Assessment of Cancer Status and Comorbidity

Cancer stage and grade were based on SEER definitions (21,22). According to SEER conventions, cancer stage is based on surgical pathology for those patients who underwent radical prostatectomy by the end of 1992. Radical prostatectomy was defined as removal of the prostate, ejaculatory ducts, and seminal vesicles, with or without dissection of pelvic lymph nodes. A total of 1209 men who were HMO members or who did not have full Medicare coverage from the time of diagnosis through the follow-up period were excluded, since their longitudinal claims histories are likely to be incomplete. We restricted the study to the three SEER regions where physician claims data were available for all Medicare beneficiaries from the CHER database; as a result, 3152 patients were excluded. In addition, 916 men who had other types of cancer diagnosed before or after the diagnosis of prostate cancer were excluded to ensure that additional cancer treatment was administered only for the management of prostate cancer. These exclusions resulted in a final sample of 3494 cases from the three geographic areas. The majority of these patients (3173) underwent radical prostatectomy within 3 months of prostate cancer diagnosis. Only eight patients had hormone therapy before radical prostatectomy.
or Gleason pattern 3; poorly differentiated/undifferentiated cancer is defined as Gleason scores 8-10 or Gleason pattern 4 or 5 (23).

A comorbidity index for each case was calculated by scoring a subset of non-cancer diagnoses appearing on inpatient claims 12 months prior to and including the admission for radical prostatectomy. The subset of medical conditions in this comorbidity index and the severity weights assigned were developed by Charlson et al. (24), using chart-based information from a cohort of breast cancer patients. We employed an automated version of the Charlson index that was originally developed by Deyo et al. (25) for use with Medicare inpatient claims.

Identification of Additional Cancer Therapy

Patients who show signs of residual cancer following radical prostatectomy or who demonstrate evidence of disease progression often receive additional therapy, such as external-beam radiotherapy and/or androgen-deprivation therapy. Androgen-deprivation therapy may include orchiectomy or treatment with estrogens, gonadotropin-releasing hormone agonists, or nonsteroidal antiandrogens. To identify patients receiving additional cancer therapy, Medicare physician claims data were searched for the presence of CPT codes 77400-77799 (radiation therapy), 54520 (orchiectomy), and 96400-96549 (injection, hormone therapy/chemotherapy). Patients undergoing orchiectomy were also identified by a search of the inpatient files for the ICD-9-CM procedure codes 62.4, 62.41, and 62.42. Patients taking self-administered prescription drugs such as diethylstilbestrol or flutamide alone could not be identified from our data sources.

Statistical Analyses

The interval between the initial treatment and any follow-up treatment was calculated from the date of radical prostatectomy to the 1st day of the follow-up cancer therapy. For men who were diagnosed during 1985-1989, follow-up was completed through the end of December 1990. For men who were diagnosed during 1990-1991, follow-up was completed through the end of December 1992. Patient follow-up was censored at death or at the last date of follow-up, whichever came first. The probabilities of additional cancer therapy were derived from Kaplan–Meier estimates (26). Cox proportional hazards regression was used to take into account censored observations and to make adjustments for several covariates simultaneously. We calculated 95% confidence intervals (CIs) for the relative risk estimates, and those values that excluded unity were interpreted to indicate statistically significant differences at a P value of less than .05. Log–log plots were used to assess the validity of the proportional hazards assumptions underlying these models, and no evidence violating the assumptions was found. Covariates included in the models were age (5-year intervals), race/ethnicity (non-Hispanic white, black, or others/unknown), comorbidity status (score 0, 1, or 2+), place of residence (Seattle–Puget Sound, Connecticut, or Atlanta), year of diagnosis (1-year intervals), cancer stage (localized, regional, distant, or unknown), and cancer grade (well differentiated, moderately differentiated, poorly differentiated/undifferentiated, or unknown). To distinguish the effects of various factors on the use of follow-up cancer treatments for residual versus recurrent disease, we carried out separate modeling for the cumulative incidence of any additional cancer therapy within and beyond 6 months of the date of radical prostatectomy. The effects of cancer grade and stage were similar within and beyond 6 months of surgery; therefore, only the overall effects are presented.

Since additional cancer treatment within 6 months of radical prostatectomy was more likely administered as adjuvant therapy or for evidence of residual disease, whereas additional cancer treatment beyond 6 months of radical prostatectomy was more likely administered for evidence of recurrent disease, we conducted separate analyses using Cox regression models. The relative risks estimated from the two separate models were similar; therefore, we combined the data from the entire study period in one analysis and present only the results from the entire study period.

Results

Table 1 shows the characteristics of the 3494 patients included in this study. Although radical prostatectomy is often reserved for men with localized prostate cancer, only 1934 (55.4%) patients had organ-confined disease on the basis of final surgical pathology. The proportion of patients undergoing radical prostatectomy with organ-confined disease remained similar during the study period: 53.8% in 1985 and 53.0% in 1991. The probabilities of requiring follow-up treatments according to age, cancer grade, and cancer stage at diagnosis are summarized in Table 2. As expected, a substantial proportion of patients who were found to have regional or distant cancer at surgery received additional cancer therapy within 6 months of surgery. Within 5 years of their initial surgery, the cumulative incidence of receiving additional cancer therapy reached 34.9% (95% CI = 31.5%-38.5%) in the study population, 24.3% (95% CI = 20.0%-29.3%) in patients with pathologically localized prostate cancer, and 49.5% (95% CI = 43.8%-55.5%) in patients with pathologically regional prostate cancer.

Since both cancer grade and cancer stage are powerful predictors of cancer progression (27-29), we stratified use of follow-up cancer treatments by these variables (Fig. 1, A and B). For the 1934 patients reported to have organ-confined disease, the 5-year probability of having any additional cancer therapy varied substantially with cancer grade: from 15.6% (95% CI = 9.7%-24.5%) for well-differentiated cancer to 41.5% (95% CI = 27.9%-58.4%) for poorly differentiated cancer (Fig. 1, A). The cumulative proportion of men with organ-confined cancer receiving additional cancer treatment within 6 months of surgery ranged from 5.4% (95% CI = 3.7%-7.8%) for well-differentiated cancer to 19.8% (95% CI = 15.2%-25.6%) for poorly differentiated cancer (Fig. 1, A).
Our study shows that, in men with regional cancer, the cumulative 5-year probability of having additional cancer therapy was relatively high, ranging from 22.7% (95% CI = 12.0%-40.5%) for well-differentiated cancer to 33.7% (95% CI = 28.9%-39.0%) for poorly differentiated cancer (Fig. 1, B). The probability of having additional cancer treatment within 6 months of surgery ranged from 12.2% (95% CI = 6.8%-21.5%) for well-differentiated cancer to 68.1% (95% CI = 58.7%-77.1%) for poorly differentiated cancer (Fig. 1, B).

Multivariate analyses revealed that patients with poorly differentiated cancer had a 3.2-fold (95% CI = 2.28-4.44) higher rate of undergoing radiation therapy and a 5.3-fold (95% CI = 2.89-9.57) higher rate of undergoing orchiectomy than patients with well-differentiated disease (Table 3). Patients with regional disease had a 2.4-fold (95% CI = 2.05-2.82) higher rate of receiving additional cancer treatment than patients whose disease was localized to the prostate (Table 3). Comorbidity status had little influence on the use of follow-up cancer therapy after radical prostatectomy (Table 3).

**Discussion**

Men with newly diagnosed, clinically localized prostate cancer face difficult treatment decisions, since the efficacy of the competing therapies is poorly defined (30,37). Few studies have addressed the need for follow-up cancer therapy after primary therapy with radical prostatectomy. Our study shows that, in three geographically defined communities, follow-up cancer treatment after radical prostatectomy reached 34.9% within 5 years of initial surgery. With time, the cumulative incidence of additional cancer treatment among men in this cohort is likely to continue to rise. The presence of other cancers cannot explain the relatively frequent use of additional cancer therapies observed in this study, since patients with other types of cancer were excluded.

These findings are consistent with the results from a national survey of Medicare patients undergoing radical prostatectomy in 1988-1990 for the management of prostate cancer (32). In that survey, 28% of patients reported that they had had radiation therapy, orchiectomy, or androgen-deprivation therapy within 4 years of their initial surgery (32). Since both the national survey and the present study used a population-based study design, the results likely reflect the experience of men treated in a broad range of settings in the fee-for-service sector and suggest that use of additional cancer treatment after radical prostatectomy was relatively common during our study period (1985-1991).

Underlying tumor biology, as measured by cancer stage and cancer grade, is the most powerful predictor of the need for additional cancer therapy, whereas patient variables, such as age and comorbidity, had little impact on the use of follow-up cancer treatments either within or beyond 6 months. The fact that almost half of the patients undergoing radical prostatectomy did not have organ-confined disease might explain the high rate of follow-up cancer treatments after radical prostatectomy. Other previously published reports (13,29,33-36) have shown similar rates of unconfined disease.
The era during which patients were diagnosed in our study, 1985-1991, partially overlapped with the period of increasing use of PSA screening for early detection of prostate cancer, which began in 1990 (37). With increased early detection and improved ability to identify patients with organ-confined cancer before surgery (38,39), the proportion of patients confirmed to have organ-confined disease at radical prostatectomy is expected to increase and eventually lower re-treatment rates. Increased use of PSA in monitoring prostate cancer progression after initial therapy, on the other hand, might increase re-treatment rates. Inclusion of men diagnosed in more recent years and longer follow-up are needed to assess the re-treatment rates in the era of widespread PSA testing.

Our results may underestimate the use of follow-up cancer treatments for various reasons. First, some patients may have received follow-up cancer therapy not recorded and reimbursed by Medicare. This fact may be particularly true for younger patients in the study cohort who may still have been working. For these patients, Medicare was often the secondary payer rather than the primary payer. Approximately 4%-5% of
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Table 3. Relative risks of having follow-up cancer treatment after radical prostatectomy, 1985-1992

<table>
<thead>
<tr>
<th>Relative risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation therapy</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Year of diagnosis: 1-year increment</td>
</tr>
<tr>
<td>0.89 (0.86-0.94)</td>
</tr>
<tr>
<td>Age, y</td>
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<tr>
<td>65-69</td>
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<tr>
<td>70-74</td>
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<tr>
<td>≥75</td>
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<tr>
<td>Race/ethnicity</td>
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<tr>
<td>Non-Hispanic white</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Others/unknown</td>
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<tr>
<td>Comorbidity score of Deyo et al. (25)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2-4</td>
</tr>
<tr>
<td>Place of residence</td>
</tr>
<tr>
<td>Seattle-Puget Sound</td>
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<tr>
<td>Connecticut</td>
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<tr>
<td>Atlanta</td>
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<tr>
<td>Cancer grade‡</td>
</tr>
<tr>
<td>Well differentiated</td>
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<tr>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>Poorly differentiated/undifferentiated</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Cancer stage based on surgical pathology</td>
</tr>
<tr>
<td>Localized</td>
</tr>
<tr>
<td>Regional</td>
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<tr>
<td>Distant</td>
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<td>Unknown</td>
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*All covariates shown in this table were included in the models.
†Referent category.
‡Cancer grade was defined as follows: well differentiated—Gleason scores 2-4 or Gleason pattern 1 or 2; moderately differentiated—Gleason scores 5-7 or Gleason pattern 3; and poorly differentiated/undifferentiated—Gleason scores 8-10 or Gleason pattern 4 or 5.

Medicare enrollees were in this category, based on 1988 data (15). Second, those men who receive care in Department of Veterans Affairs (VA) hospitals may have missing information on follow-up treatments. Hospitalizations for selected conditions in VA hospitals accounted for 3.6% of all such hospitalizations in Medicare-eligible men (40). Finally, the use of androgen-deprivation therapy is likely to be underestimated, since simple prescriptions for oral estrogens and nonsteroidal antiandrogen are not covered by Medicare, and some patients may have been treated with these agents during the study period.

Despite this underestimation, the cumulative incidence of re-treatment remained relatively high even among patients with pathologically organ-confined cancer, ranging from 15.6% for well-differentiated cancer to 41.5% for poorly differentiated cancer. These patients are usually considered optimal candidates for radical prostatectomy. Because of the limitations of the data, we could not identify the indications for the use of follow-up treatments. Follow-up cancer therapy administered within 6 months of surgery more likely represents adjuvant therapy or treatment of residual cancer, whereas the use of follow-up cancer treatment beyond 6 months of surgery more likely represents recurrent cancer, although some may well reflect additional adjuvant therapy. Selected academic centers have reported more favorable results than we observed in this study. For example, the 5-year risk of cancer recurrence as measured by PSA failure among patients with pathologically organ-confined cancer was reported to be 8%-9% in selected medical centers (12,13). In comparison, up to 24% of patients with pathologically localized cancer based on SEER staging criteria received additional cancer treatment within 5 years of surgery; 8.6% received additional treatment within 6 months of surgery, whereas an additional 16.9% received re-treatment between 7 and 60 months. Potential factors for the discrepancy include differences in case selection, surgical skills, and practice patterns regarding the use of adjuvant therapy. It is less certain whether the high re-treatment rates, particularly among patients with pathologically localized cancers, could be attributed to suboptimal pathologic examinations in the diverse settings (both community and academic centers) represented in these SEER areas. Because of lack of a "gold standard," we could not assess the validity of cancer staging and grading as recorded in the SEER database. However, if some cancers reported as pathologically localized cancers were indeed unconfined, the proportion of organ-confined cancers would be even lower than the 55.4% figure we report. Although we cannot determine to what extent each of the listed factors contributed to the observed discrepancy, it is clear that the frequency of re-treatment reported by selected medical centers cannot be generalized to the entire population of men undergoing radical prostatectomy and that the use of additional cancer therapy after radical prostatectomy is more common than what has been reported in the literature (12,13).
Adjuvant therapy is commonly used in the management of cancer. However, its role in the management of prostate cancer remains to be defined (14). Reports of low re-treatment rates after radical prostatectomy may have led many patients to believe that radical prostatectomy alone is sufficient for managing their prostate cancer. Since the likelihood of requiring additional cancer treatment after initial therapy might influence their treatment decisions, it is important that patients be informed of the re-treatment rates based on the experience of men treated in a spectrum of community settings as well as men treated at selected academic medical centers. Given the wide use of follow-up cancer treatments after initial surgery and the uncertainties concerning the value of these treatments (14), the effectiveness of various follow-up treatment strategies after radical prostatectomy warrants further investigations.

References

(8) Barry MJ. Proving early detection and treatment of prostate cancer does more good than harm: the need to support randomized trials actively [editorial; comment] [see comment citations in Medline]. J Urol 1994;152(5 Pt 2):1903-4.

(35) Ancher MS, Prostznitz LR. Postoperative radiotherapy for patients with carcinoma of the prostate undergoing radical prostatectomy with positive surgical margins, seminal vesicle involvement and/or penetration through the capsule. J Urol 1987;138:1407-12.
(38) Catalona WJ, Smith DS, Ratitiff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based testing [see comment citation in Medline]. JAMA 1993;270:948-54.
(39) Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer [see comment citation in Medline]. JAMA 1994;271:368-74.

Notes

1 Editor’s note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry
The p53 Gene in Breast Cancer: Prognostic Value of Complementary DNA Sequencing Versus Immunohistochemistry

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**Background:** Mutations in the p53 tumor suppressor gene (also known as TP53) have been detected in a wide variety of human cancers. In breast cancer, the presence of p53 gene alterations has been associated with worse prognosis. **Purpose:** We compared a complementary DNA (cDNA)-based sequencing method and an immunohistochemical (IHC) method for their abilities to detect p53 mutations in breast cancer specimens. In addition, we determined the prognostic value of information obtained when these two methods were used. **Methods:** Specimens from 316 primary breast tumors were evaluated for the presence of mutant p53 protein by use of the mouse monoclonal antibody Pab 1801 (that recognizes both wild-type and mutant forms of p53) and standard IHC methods. In addition, the entire coding region of p53 genes expressed in these tumors was screened for mutations by combining reverse transcription, the polymerase chain reaction, and DNA sequencing. Probabilities for overall survival (OS), breast cancer-corrected survival (BCCS; death from breast cancer is the considered event), and relapse-free survival (RFS) were estimated by use of the Kaplan–Meier method, and survival curves for different patient subgroups were compared by use of the logrank method. All reported *p* values are from two-sided tests. **Results:** Sixty-nine (22%) of 316 tumors had p53 gene mutations detected by the cDNA-based sequencing method; only 31 (45%) of these mutations were located in evolutionarily conserved portions of the p53 coding region. Sixty-four tumors (20% of the total) had elevated levels of p53 protein as detected by IHC, suggesting the presence of mutations. Of the sequencing-positive tumors (i.e., p53 mutant), 23 exhibited negative IHC reactions, indicating that IHC failed to detect 33% of the mutations. Furthermore, 19 of the IHC-positive tumors were sequencing negative (i.e., p53 wild-type), suggesting a 30% false-positive frequency with IHC. Four tumors (1.3% of the total) could not be analyzed by the cDNA-based sequencing method, and three tumors (1% of the total) could not be analyzed by IHC. The 5-year estimates for RFS, BCCS, and OS were significantly shorter for patients with p53 sequencing-positive tumors than for patients with sequencing-negative tumors (*P* = .001, *P* = .01, and *P* = .0003, respectively). Patients with IHC-positive tumors showed reduced survival in all three categories when compared with those with IHC-negative tumors, but the differences were not statistically significant. **Conclusions:** Use of a cDNA-based sequencing method to determine the status of the p53 gene in primary breast cancers yielded better prognostic information than IHC performed with the Pab 1801 monoclonal antibody. [J Natl Cancer Inst 1996;88:173-82]

Alteration of the tumor suppressor gene p53 (also known as TP53) is considered to be a critical step in the development of many human cancers (1,2). Changes in this gene have been detected in a wide range of human tumors, including breast cancers (3). The p53 gene is located on chromosome 17p, and its product is a nuclear phosphoprotein. The p53 protein has been identified as a transcription factor with sequence-specific DNA-binding properties and an ability to regulate entry into S phase of the cell cycle (3-5). The p53 protein has also been shown to influence the induction of apoptosis in malignant cells (6).

In breast cancer, research has focused on patients with primary, node-negative breast disease, and alterations in the p53 gene have been associated with worse prognosis (7-9).

Previous studies (8,10-18) evaluating p53 status in cancer have used single-stranded conformation polymorphism analysis (SSCP), DNA sequence analysis, or immunohistochemistry (IHC). Detection of p53 mutations by IHC is based on the ac-