Long-Term Survival in Men With High Grade Prostate Cancer: A Comparison Between Conservative Treatment, Radiation Therapy and Radical Prostatectomy—A Propensity Scoring Approach

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Purpose: We performed a retrospective cohort study using propensity score analysis to calculate long-term survival in patients with prostate cancer with Gleason score 8 or greater who were treated with conservative therapy, radiation therapy and radical prostatectomy.

Materials and Methods: Between January 1, 1980 and December 31, 1997, 3,159 patients in the Henry Ford Health System were diagnosed with clinically localized prostate cancer. Of these patients 453 had a Gleason score of 8 or greater in the biopsy specimen and they were the cohort. The end points were overall and prostate cancer specific survival. Propensity score analysis was used to more precisely compare the 3 treatments of observation, radiation and radical prostatectomy. Median patient followup was longer in the radical prostatectomy arm than in the conservative treatment and radiation therapy arms (68 months vs 52 and 54, respectively).

Results: Of the 453 patients 197 (44%) were treated conservatively, 137 (30%) received radiation therapy and 119 (26%) underwent radical prostatectomy. Using propensity scoring analysis median overall survival for conservative therapy, radiation and radical prostatectomy was 5.2, 6.7 and 9.7 years, respectively. Median cancer specific survival was 7.8 years for conservative therapy and more than 14 years for radiation therapy and radical prostatectomy. The risk of cancer specific death following radical prostatectomy was 68% lower than for conservative treatment and 49% lower than for radiation therapy (p <0.001 and 0.053, respectively).

Conclusions: Survival of men with high grade prostate cancer can be improved by radical prostatectomy or radiation therapy.

Key Words: prostate, prostatic neoplasms, mortality, prostatectomy, radiotherapy

In 2006 approximately 234,000 men were diagnosed with prostate cancer in the United States. While some prostate cancers are biologically indolent, Gleason score 8–10 cancers are aggressive, often resulting in early metastasis, significant morbidity and eventual mortality. When left untreated, up to 85% of these men die of prostate cancer within 10 years of diagnosis.1 High grade cancers are also unique because they can affect younger males, produce less PSA and have relative resistance to radiation.2 Cancer control is difficult to achieve, and physicians and patients are uncertain what the best management approach is for these patients.

To address this question we performed a single center, retrospective cohort study measuring long-term survival in men with high grade prostate cancer after adjusting for age, race, stage, year of diagnosis, serum PSA, comorbidities and the treatment received. The 3 standard treatments evaluated were conservative treatment or watchful waiting, RT and RP. We used propensity score analysis to more accurately compare these 3 treatment modalities. This approach minimizes the selection bias inherent in retrospective cohort studies by creating risk quintiles to match subjects across treatment groups.3–6 Our end points were overall survival and cancer specific survival.

MATERIALS AND METHODS

Setting
The study was performed at HFHS, a vertically integrated health system incorporating the tenth largest health maintenance organization in the nation. The population served by HFHS is large and diverse, including approximately 30% black Americans. HFHS has a computerized medical information and records system, and comprehensive use data are available from computerized health claims databases. HFHS maintains a computerized tumor registry database accredited by the American College of Surgeons. Registry staff uses a thorough case finding system that reviews all pathology and cytology reports as well as radiation and oncology consultations. HFHS registry staff link this data with Detroit area Surveillance, Epidemiology and End Results program records, and perform annual followup (estimated at 94%) for vital status and recurrence.
Cohort Establishment

**Inclusion criteria.** The HFHS tumor registry was queried for all patients with an ICD code of 185 (prostate cancer) who were treated and followed from January 1, 1980 to December 31, 1997. The diagnosis of cancer was established by initial histological examination of prostate biopsy specimens by HFHS pathologists. Tumor grade was reported as 1—well differentiated, Gleason score 2–4, 2—moderately differentiated, Gleason 5–7 or 3—poorly differentiated, Gleason 8–10. There was no re-review of archived pathological materials. While pathological tumor grades from prostatectomy specimens were available, they were specific only to patients who underwent RP and, therefore, they were not used. Only men with localized (negative bone scan or computerized tomography) high grade (grade III or Gleason 8–10) cancer were included in the study. All patients in the study underwent bone scan.

**Exclusion criteria.** We excluded patients who were older than 75 years, had low grade cancer (grades I or II, Gleason score less than 8) or had incomplete followup. In addition, patients with bone metastasis within 1 year of diagnosis were excluded because we believed that these men most likely had preexisting metastatic disease.

**Related variables.** To study the impact of various treatments we collected information about clinically significant baseline variables known to affect long-term survival, such as age, year of diagnosis, year of treatment, race, comorbidity, stage, baseline serum PSA and ZIP code of residence, which is a surrogate for socioeconomic status. Staging was done using the 1992 TNM classification. PSA testing was widely introduced in our study population in 1990. Therefore, we performed subgroup analysis for patients who had baseline PSA measurements available. The results are presented separately.

**Ascertainment of comorbidity.** Comorbidity was assessed by electronically searching for previously published comorbid conditions by ICD code. Detailed comorbidity information was missing from 1980 to 1987. Using previously published methodology we determined the comorbidity for this duration by accounting for patient age and race. Sensitivity analysis of comorbidity measurements during the 2 periods 1980 to 1987 vs 1988 to 1997 did not reveal any statistical differences. These comorbidities were then used to calculate a validated modified comorbidity index, as described by Charlson et al.7

**Cohort followup (vital statistics).** Vital statistics were gathered from state health department death certificates and through linkage with the National Death Index. The vital status of all living patients was confirmed, verified and quality checked through telephone interviews, examination of medical records, Health System corporate data stores, the Surveillance, Epidemiology and End Results database for Michigan, mailed reminders and hospital visit documentation.

**Cohort description.** The data sources identified 4,387 patients with localized prostate cancer, of whom 1,012 were older than 75 years and 4 were neither black nor white. These men were excluded from analysis. Of the remaining 3,371 men biopsy grade or income information was incomplete in 212. Thus, complete information was available in 3,159 men, of whom 453 had high grade cancer. They form the study cohort.

**End Points**

The end points of these analyses were death from all causes and death from prostate cancer. A man died of prostate cancer if prostate cancer (ICD-9th edition, code 185) was listed as the primary or contributing cause of death, ie it appeared on the first 3 lines of the death certificate.1

**Statistical Analysis**

**Propensity score modeling.** The use of observational studies to compare different treatment options has inherent limitations. To make more valid treatment comparisons in a retrospective cohort setting we performed propensity score analysis, which is a methodology that reduces confounders to a single composite variable rather than accounting for each of them individually. This allowed us to group patients with similar characteristics into risk quintiles and match the subject across treatment groups. This minimizes the inherent selection bias in retrospective cohort studies and enabled us to perform a form of randomization.3–6

In our study linear discriminant analysis was used to calculate propensity scores for treatment by surgery and by RT as a function of baseline patient age, race, Charlson comorbidity score, grade, year of diagnosis and estimated income. Linear discriminant functions correctly classified the treatment group in 54.4% of patients, including 60.5% of those choosing surgery, 52.5% of those choosing RT and 50.3% of those choosing watchful waiting.

**Survival analysis.** We adjusted for baseline variables that predicted mortality and used intent to treat analysis (all patients who had positive lymph nodes on lymphadenectomy remained in the prostatectomy arm).9 Analyses of outcomes were based on primary treatment assignment. Comparisons of mortality rates were based on survival analysis and they used the Cox proportional hazards model. All relative risks were obtained from the multivariate Cox models. Adjusted survival curves were generated using the empirical cumulative hazard estimate of the survivor function. Differences in the duration of survival were calculated by measuring differences in adjusted survival curves at median survival.9 All p values are 2-sided. Statistical analysis was performed with SAS®, version 8.2.

**RESULTS**

**Characteristics of the Study Population**

Table 1 shows the study population. Patients treated with RT were older than men treated conservatively or with RP (mean ± SD age 68.0 ± 5.8 vs 60.0 ± 5.7 and 62.9 ± 6.2) and they also had more comorbidities (RT, conservative management and RP Charlson scores 1.81 ± 1.51, 1.44 ± 1.26 and 1.23 ± 1.21, respectively). Black patients represented 57.6% of the study group and they were less likely to undergo RP than white patients (20.0% vs 31.0%). Median patient followup was longer for the RP arm than for conservative treatment and RT (68 months, range 3.7 to 174 vs 52, range less than 1 to 227 and 54, range 8.4 to 206, respectively).
Hormonal Therapy
Overall 285 patients received hormonal therapy within 6 months of prostate cancer diagnosis. A significantly greater percent of patients in the conservative treatment arm received hormonal therapy than in the RT and RP arms (40.6% vs 19% and 18.5%, respectively). There were no differences in survival between patients who did and did not receive hormonal therapy in the 3 treatment groups. These results are presented separately.

Treatment Outcomes
Death from any cause. Table 2 shows the adjusted and unadjusted 15-year relative risk of overall death in patients undergoing the different types of treatment (part A of figure). After propensity score (multivariate) analysis patients receiving RP had significantly lower risk ratios than patients treated conservatively or with RT. Each RP propensity quintile had a 50% lower risk than other quintiles. The risk of overall death following RP was 68% lower than with conservative management and 49% lower than with RT. Propensity adjusted 10-year survival. Table 3 shows crude and adjusted overall and cancer specific survival in patients with high grade disease undergoing RP and RT. It should be noted that the 2 modalities decreased the risk of death in these patients.

DISCUSSION
Prostate cancer is a unique malignancy. Biological behavior varies significantly among various cancer grades. Low and moderate grade cancers grow slowly, while high grade cancers behave quite aggressively and they are reported to result in lymph node metastasis in up to 60% of patients.10 In our study approximately 50% of patients with high grade cancers died within 15 years of diagnosis. Of the deceased patients more than 50% died of prostate cancer.

Considerable controversy and confusion surround the appropriate treatment for newly diagnosed, high grade, localized prostate cancer. Pessimism exists among clinicians be-
cause they believe that such tumors are beyond cure and, thus, they often recommend conservative treatment, such as watchful waiting or early hormonal therapy. Radiation oncologists often think that these tumors are radio resistant, while many surgeons avoid treating these patients due to a perceived modest survival advantage. There is even a paucity of published treatment trends for high grade prostate cancer. Ultimately randomized trials of the long-term outcomes of these 3 treatment approaches are necessary to lift this shroud of uncertainty. It is important that these studies should focus on overall and cancer specific survival. While assessment of overall survival can be confounded by unmeasured factors and cancer specific mortality can be potentially biased by differential assignments for cause of death depending on initial treatment, these end points are preferable to surrogate outcomes such as biochemical recurrence, which have often failed to correlate with ultimate survival.

While 2 randomized studies are under way to compare the results of surgical therapy with those of watchful waiting, they focus on all grades rather than on only high grade cancers. The studies also do not include RT in the comparisons, nor did the Prostate Cancer Intervention Versus Observation Trial in the United States, which closed accrual last year. Results from the Scandinavian study are available but they have no black American representation and the study excluded high grade cancers. Therefore, we think that a single center, equal access system cohort study using propensity score analysis can serve as a useful source of information regarding long-term outcome in patients with high grade cancer.

### High Grade Cancer and Conservative Treatment
Albertsen et al reported a 15-year analysis of a population based cohort of 767 men treated conservatively for localized prostate cancer. Approximately 10% of these men had high grade cancer and they had a 15-year disease specific survival rate of between 13% and 40%. Aus et al reported a retrospective analysis of 301 Swedish men with localized prostate cancer in which high grade tumors were clearly the most fatal with a mortality rate of 60% and a 10-year cause specific survival rate of 19%. In a pooled analysis of 828 men treated conservatively Chodak et al found a 34% 10-year disease specific survival rate in men with a similar Gleason grouping, of whom the majority had T1/T2 stage disease. Our current study shows a similar overall survival rate of 30%. It goes a step further by being able to compare survival and inversely the risk of death with that in patients undergoing RT or RP. Each treatment significantly decreased the overall risk of death compared to conservative management.

### High Grade Cancer and RT
The RT Oncology Group performed 4 prospective, randomized trials for clinically localized prostate cancer and noted that Gleason score was the strongest predictor of overall and disease specific survival. Pooled analysis of 1,560 patients from various radiation studies showed a rate of 27% for Gleason 8-10 prostate cancers with 25% 10-year overall survival and 44% 10-year disease specific survival. These published results show worse survival than the 58% overall survival reported in our study. However, this discrepancy is most likely due to the inclusion of up to 59% T3 cancers in the RT Oncology Group studies. On multivariate analysis
our study showed that radiotherapy significantly improved overall survival by 30% compared with conservative treatment but it did not significantly increase cancer specific survival.

High Grade Cancer and RP
Cancer specific survival in our series in patients who underwent RP was 77%, identical to that in a multi-institutional analysis of 2,758 men with clinically localized prostate cancer treated with radical retropubic prostatectomy, as described in 1996 by Gerber et al. Lu-Yao and Yao, and Hull et al reported comparable results (67% and 75%, respectively). In a recent study from Mayo Clinic Lau et al identified 407 patients with pathological Gleason 8 or greater prostate cancer and reported 67% overall 10-year survival and 85% 10-year cancer specific survival. Only 26% of the cases were pT2 and the remainder were pT3 or pTxN+. However, comparison to our study is difficult because we used biopsy rather than pathological Gleason grade due to our additional consideration of conservative management and RT. Another recent Mayo Clinic study showed 20-year cancer specific survival rates of 58% to 64% in 73 patients with Gleason 8–10 undergoing RP. This study had approximately 15% clinical stage T3 cancers, which are known to have poorer prognosis.

In diseases such as high grade prostate cancer, for which randomized studies are nonexistent or do not include all treatment groups, it is appropriate to resort to observational studies and attempt to decrease their inherent biases to help patients and clinicians assess and compare treatment risks more accurately. With this aim in mind we used propensity scoring methodology, a valid statistical approach that has been used in several such studies, enabling us to compare all 3 treatment modalities. We noted that for a given quintile the overall risk of death in patients undergoing RP was 68% lower than in those with conservative treatment and 54% lower than in those with RT.

Our study strengths are its large database, intent to treat analysis, propensity score modeling, representation of black race, single institution setting, capture of comorbidity and adjustment for baseline confounders. Therefore, the findings are a useful addition to the existing literature.

CONCLUSIONS
Even high grade cancers are potentially curable. Retrospectively there is a significant difference in long-term outcome among patients undergoing conservative treatment, RT and RP.

Abbreviations and Acronyms

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<tr>
<td>HFHS</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>PSA</td>
<td>prostate specific antigen</td>
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<td>RP</td>
<td>radical prostatectomy</td>
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