National Trends in the Management of Low and Intermediate Risk Prostate Cancer in the United States

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Purpose: To our knowledge factors affecting the adoption of noncurative initial management in the United States for low risk prostate cancer on a population based level are unknown. We measured temporal trends in the proportion of patients with low and intermediate risk prostate cancer who elected noncurative initial treatment in the United States and analyzed the association of factors affecting management choice.

Materials and Methods: We identified 465,591 and 237,257 men diagnosed with low or intermediate risk prostate cancer using NCDB and SEER (2004 to 2010), respectively. We measured the proportion of men who elected noncurative initial treatment and used multivariate logistic regression analysis to evaluate factors affecting the treatment choice.

Results: During the study period noncurative initial management increased in patients at low risk from 21% to 32% in SEER and from 13% to 20% in NCDB (each p < 0.001). This increase was not reflected in our overall study population (SEER 20% to 22% and NCDB 11% to 13%) since the proportion of patients with Gleason score 6 or less decreased with time (61% to 49% and 61% to 45%, respectively). From 2004 to 2010 older age, lower prostate specific antigen, earlier clinical stage, increased comorbidity index and not being married were associated with a higher likelihood of noncurative initial management (each p < 0.05).

Conclusions: Two independently managed, population based data sets confirmed a temporal increase in noncurative initial management in patients with low risk PCa that did not translate into greater use overall in those at low and intermediate risk combined. These contrasting results are likely due to grade migration resulting in fewer men being classified as with low risk PCa based on Gleason score.

Key Words: prostate, prostatic neoplasms, SEER program, risk, trends

In an 18-year followup report of men with localized PCa the risk of non-cancer death was dramatically higher than that of PCa death, especially in patients at low risk.1 To decrease overtreatment and potential treatment associated morbidity multiple groups have investigated NCIM approaches in select patients.2–4 A NCIM strategy termed active surveillance showed approximately 97% cancer specific survival 10 years after diagnosis with most men remaining on observation and not requiring surgery or radiation.5 This growing body of evidence prompted multiple guidelines to recognize NCIM as a strategy for low risk PCa, defined as PSA less than 10 ng/ml, Gleason score 6 or less and cT1-T2a.5–7

Abbreviations and Acronyms

ADT = androgen deprivation therapy
CCI = Deyo-Charlson comorbidity index
NCDB = National Cancer Database
NCIM = noncurative initial management
NOS = not otherwise specified
PCa = prostate cancer
PSA = prostate specific antigen
SEER = Surveillance, Epidemiology and End Results

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NCIM adoption through 2004 was modest with 1 study showing a rate of less than 10% in low risk cases. In addition, ISUP (International Society of Urological Pathology) modified the Gleason scoring system in an effort to homogenize the definition of Gleason pattern 3 by making any cribriform pattern Gleason 4. This may explain the recent grade migration in the United States, leading to fewer cases qualifying as low risk Gleason 6. Normally attributable to patient preference, NCIM underuse was highlighted in a 2011 NIH (National Institutes of Health) consensus statement. It mentioned patient and societal factors as important aspects of future research to understand decision making for low risk PCa management.

We used 2 independently managed national databases to analyze the characteristics of patients with low and intermediate risk PCAs between 2004 and 2010. We determined the proportion of men who met eligibility criteria for and elected NCIM, and we evaluated factors affecting the choice of NCIM.

MATERIALS AND METHODS
After acquiring institutional review board exemption we extracted data on 2004 to 2010 from SEER and NCDB. SEER represents 28% of cancers in the United States and captures all cancers in 18 defined geographic regions. NCDB acquires data on 70% of cancers in the United States and represents 28% of cancers in the United States. We identified all patients diagnosed with non-metastatic PCAs (SEER 388,425 and NCDB 846,965), PSA 20 ng/ml or less (SEER 64,124, information missing on 324,301 and NCDB 119,903, information missing on 658,952), Gleason score less than 8 (SEER 14,518, information missing on 846,965) and cT1-2 disease (SEER 2,124, information missing on 241,370 and NCDB 59,968, information missing on 470,669) as well as known data on treatment (SEER 237,271 and NCDB 465,591) and patient age (SEER 37,257 and NCDB 465,591) Although each database extends through 2011, data on patients diagnosed in 2011 were not analyzed because at least a year of followup was required to determine initial treatment.

Using National Comprehensive Cancer Network® risk groups low risk PCa was defined as PSA less than 10 ng/ml with Gleason score 6 or less. In NCDB and SEER PSA is recorded as the highest value before the diagnostic procedure or if unavailable the earliest pretreatment but post-diagnostic value. Before 2010 Gleason score was recorded in each database as clinical grade or if available pathological grade after radical prostatectomy. For consistency we used this method for patients diagnosed in 2010. Cases with PSA 10 to 20 ng/ml or Gleason 7 were labeled as intermediate risk.

Primary treatment was defined as management within 1 year of diagnosis. Radiation included external beam radiotherapy or brachytherapy. The code for surgery shared by the databases included prostatectomy, cryosurgery, laser ablation and hyperthermia, and transurethral resection of the prostate. Because transurethral prostate resection has no curative intent, it was not considered surgery.

In SEER if neither surgery nor radiation was indicated, a NCIM approach such as active surveillance or passive watchful waiting was considered the management strategy. In NCDB ADT is also recorded and it was not considered NCIM. NCDB also allowed us to determine the time between diagnosis and all treatments. We performed sensitivity analysis defining NCIM as no treatment for 6 months to determine whether the NCIM trends were similar with a less conservative cutoff.

Patient, cancer, temporal and geographic factors were analyzed for an association with NCIM. The factors included age, marital status, race, clinical stage, PSA, CCI, diagnosis year and geographic location. In SEER married and unmarried/domestic partner patients were considered married while single, separated, divorced or widowed patients were labeled not married. Facility type was based on the number of patients with PCa encountered each year, including community—greater than 100, comprehensive—greater than 500 and academic—greater than 500 with graduate medical training offered.

Multivariate logistic regression analysis was done to determine relationships between independent variables and NCIM use as the dependent variable. All variables measured were included on the final multivariate analysis. Additional multivariate logistic regression analysis was performed to compare the proportion of men with low risk PSA (less than 10 ng/ml), Gleason score (6 or less) or nonpalpable clinical stage (T1) by independent variable diagnosis year (2010 vs 2004). To account for temporal changes in age and race they were also included as independent variables on analysis. All ORs and p values were derived from our multivariate logistic regression analysis with p < 0.05 considered statistically significant. All statistical analysis was done with STATA® 12.0 software using the logistic command for all multivariate analyses.

RESULTS
Supplementary table 1 (http://jurology.com/) shows initial management, demographics and tumor characteristics. In each data set almost half of the patients were diagnosed between ages 60 and 69 years, and approximately 70% were white non-Hispanic. Most patients with low risk PCa (SEER 77.1% and NCDB 60.3%) and intermediate risk PCa (58.9% and 60.3%, respectively) had PSA between 4 and 10 ng/ml.

NCIM use in men with low risk PCa in SEER increased from 21% (3,630 of 16,960) to 32% (5,020 of 15,510) (2010 vs 2004 OR 1.89, 95% CI 1.79–1.99, p < 0.001, supplementary table 2, http://jurology.com/ and fig. 1, A). NCIM in men with intermediate risk PCa decreased from 18% to 14% (2010 vs 2004 OR 0.91, 95% CI 0.86–0.97, p = 0.006,
supplementary table 2, http://jurology.com/ and fig. 2, A). In the entire cohort of men with PCa the NCIM rate remained stable with time at about 20% (supplementary table 2, http://jurology.com/ and fig. 3, A). Similarly in NCDB NCIM use in men with low risk PCa increased from 13% (3,945 of 31,158) to 20% (5,582 of 28,028) (2010 vs 2004 OR 1.93, 95% CI 1.84–2.02, p < 0.001, supplementary table 3, http://jurology.com/ and fig. 1, B). NCIM in men with intermediate risk PCa remained stable at about 9% and yet diagnosis year was a positive predictor of NCIM (2010 vs 2004 OR 1.18, 95% CI 1.12–1.25, p < 0.001, supplementary table 3, http://jurology.com/ and fig. 2, B). NCIM in all men increased slightly with time from 11% to 13% (supplementary

Figure 1. Trends in low risk PCa treatment from 2004 to 2010. Unadjusted rates of treatment within 1 year of diagnosis were measured. In SEER NCIM was assumed if neither surgery nor radiation was indicated (A). In NCDB NCIM was assumed if no active treatment such as surgery, radiation or ADT was indicated (B).
On sensitivity analysis using 6 months of no treatment as the NCIM cutoff NCIM increased from 23% to 28%, decreased from 20% to 16% and decreased slightly from 22% to 21% in men at low and intermediate risk, and all men, respectively.

When men with cT2NOS were excluded from analysis, the measured NCIM rates were 2% and 0.1% less in SEER and NCDB, respectively, during the entire study period (data not shown).

In SEER radiation use decreased in patients with low risk (44% to 34%) and intermediate risk (39% to 34%) PCa, and overall (42% to 34%) (figs. 1 to 3). Surgery decreased slightly in low risk cases (34% to 33%) and increased in intermediate risk cases (41% to 49%) and overall (37% to 42%).
Similarly in NCDB radiation use decreased in men with low risk (54% to 33%) and intermediate risk (50% to 30%) PCa, and overall (52% to 31%) (figs. 1 to 3). Surgery use increased in men with low risk (31% to 46%) and intermediate risk (36% to 59%) PCa, and overall (33% to 53%). ADT use decreased in men with low risk (1.9% to 0.8%) and intermediate risk (3.0% to 1.2%) PCa, and overall (2.5% to 1.0%).

In SEER and NCDB in all men with low and intermediate risk cancer there were increases in the proportion with stage cT1 and PSA less than 10 ng/ml, and a decrease in Gleason score 6 or less (2010 vs 2004 adjusting for age and race each

**Figure 3.** Trends in low and intermediate risk PCa treatment from 2004 to 2010. Unadjusted rates of treatment within 1 year of diagnosis were measured. In SEER NCIM was assumed if neither surgery nor radiation was indicated (A). In NCDB NCIM was assumed if no active treatment such as surgery, radiation or ADT was indicated (B).
In the current study in men with in-
diagnosis year and higher CCI, and those who were
notably men with older age, lower PSA, a more recent
NCIM with time in men with low risk PCa, most
each database.

therapy and increases in surgery were noted in
those at intermediate risk. Decreases in radiation
NCIM remained stable or decreased slightly in
in NCIM in patients with low risk PCa while
bases demonstrated large unadjusted increases
clinical stage were predictors of NCIM. The 2 da-
ners in a single study elim-

p <0.001, supplementary figure, http://jurology.com/).
Consequently the proportion of men with low risk
Gleason score plus PSA decreased from 52% to 44%
in SEER (2010 vs 2004 OR 0.71, 95% CI 0.69–0.73)
and from 54% to 41% in NCDB (2010 vs 2004 OR
0.57, 95% CI 0.55–0.58, each p <0.001). Low risk
NCIM increased in SEER by 11% and in NCDB by
7%. However, if the same proportion of men who
qualified as at low risk in 2004 were at low risk in
2010, the increase in low risk NCIM would be only
6% (21% or 3,630 of 16,960 in 2004 and 27% or
5,020 of 18,362 in 2010) in SEER and 2% (13% or
3,945 of 31,158 in 2004 and 15% or 5,582 of 36,930
in 2010) in NCDB.

In low risk cases in SEER and NCDB the more
recent diagnosis year (2010 vs 2004), increasing age
(greater than 74 vs less than 50 years), lower clin-
ical stage (cT2 vs cT1), lower PSA (4.1 to 10 ng/ml vs
4.0 or less) and race (white vs black) predicted
greater NCIM use (p <0.001), except clinical stage
in SEER (p = 0.018, supplementary tables 2 and 3,
http://jurology.com/). In SEER nonmarried status
also predicted NCIM (p <0.001, supplementary
table 2, http://jurology.com/). Unique predictors of
NCIM in NCDB were community facility (vs
comprehensive), Medicare insurance (vs private
insurance) and increased CCI (greater than 1 vs 0)
(each p <0.001, supplementary table 3, http://
jurology.com/).

DISCUSSION
We analyzed trends in NCIM use for low and in-
termediate risk PCAs. NCIM is now a recommended
management option in patients with low risk PCAs
to mitigate the potential harms of overtreatment.
Using population based data from SEER and
NCDB we observed that older age, recent diag-
nosis year, lower Gleason score, lower PSA and
clinical stage were predictors of NCIM. The 2 da-
atabases demonstrated large unadjusted increases
in NCIM in patients with low risk PCAs while
NCIM remained stable or decreased slightly in
those at intermediate risk. Decreases in radiation
therapy and increases in surgery were noted in
each database.

Data from Sweden showed similar increases in
NCIM with time in men with low risk PCAs, most
notably men with older age, lower PSA, a more recent
diagnosis year and higher CCI, and those who were
unmarried.19 In the current study in men with in-
termediate risk PCAs PSA 10 to 20 ng/ml predicted
greater NCIM use than PSA 0.1 to 2.5 ng/ml.
Although we have no clinically sensible explanation
for this observation, Swedish data also revealed
increased NCIM use in patients with intermediate
risk PCAs with higher PSA.19

Temporal trends in NCIM in men with low risk
PCAs are encouraging, given the demonstrated
safety of active surveillance in this group, and the
trends may be due to increased awareness due to
updated data and guidelines.2,3,5–7 The increase in
NCIM also appears to be replacing radiation ther-
rapy. It was unclear in the current study whether
this represents a general transition away from
considering radiation for low risk PCAs.

Despite the trends NCIM remained low in sur-
veillance candidates (20% to 32%). In addition,
the proportion of men with low risk PSA and low
Gleason score decreased in our study population
and in all patients with localized PCas in the United
States.10 The decrease in low risk cases appears to
have been due to ongoing Gleason grade migration,
leading to fewer cases of Gleason score 6 or less.19

Grade migration, which is likely the result of 2005
Gleason grade modifications increasing the homo-
genicity of Gleason 6 cancer, may lead to spuriously
improved survival rates via the Will Rogers phe-
nomenon.9 However, fewer men will qualify as at low
risk, contributing to NCIM underuse, as evidenced
by the nominal 0% to 2% increase in the rate of
NCIM when men with low and intermediate risk
PCAs were combined. This finding demonstrates a
statistical artifact that is evocative of the original
Will Rogers phenomenon, that is an inflated large
increase in the rate of a recommended treatment in
1 risk group while the overall rate of that treatment
remains unchanged.

In men at intermediate risk in 2010 SEER
showed a slight decrease while NCDB showed a
slight increase in the odds of NCIM. This discrep-
ancy may have been due to decreasing ADT mono-
therapy use in patients in SEER, which cannot be
separated from NCIM using SEER coding. NCDB
demonstrated a 2% decrease in ADT monotherapy
in men at intermediate risk. The true trend likely
lies between the 2 possibilities, that is there has
been little to no change in NCIM. This finding is
relevant since more men are being diagnosed with
intermediate risk disease.10 In other words, there
appears to be an unchanging proportion of NCIM in
men with PSA greater than 10 ng/ml or Gleason
score greater than 6. Importantly our findings pro-
vide the impetus to continue investigating the
safety of active surveillance in select patients with
intermediate risk PCAs.20

A strength of our study is the population based
nature of SEER and NCDB. Although the 2 data-
bases differ in exact numbers, their congruence on
temporal trends and ORs supports our conclusions.
The unity of the 2 databases in a single study elim-
nates the shortcomings inherent to either database.
For instance, only SEER includes information on
marital status while only NCDB records CCI, facility
type and insurance type. Additionally, NCDB predominately comprises patients treated at academic and comprehensive facilities while SEER captures all cancers diagnosed in defined geographic regions. Therefore, patients in NCDB may be more likely to be referred from community practices and have higher risk PCs. Also, although we attempted to combine regions in the databases into similar areas, each database unavoidably collects data from locations where data are not collected by the other database. This may account for the discrepancies between the 2 databases related to region and NCIM odds. Also, the accentuated decrease in radiation therapy in NCDB was likely the result of increasing radiation therapy use in physician offices relative to hospitals. Finally, while SEER does not provide information on ADT monotherapy, in NCDB ADT accounted for 1.6% of low and intermediate risk cases.

Our study is not without limitations. About 21% and 25% of men with nonmetastatic PCs were excluded from study due to missing risk criteria in SEER and NCDB, respectively. Excluding these patients in SEER may have biased our cohort toward certain geographic regions and younger men. To minimize potential biases in treatment trends we did not exclude patients with clinical stage cT2NOS from analysis but cT2NOS may include any cT2 and some cT1. While this heterogeneous group composed 21% of our SEER cohort, it represented only 4% of NCDB. This likely accounts for differences in the odds of NCIM based on clinical stage between the databases. Notably, excluding men with cT2NOS did not change the overall NCIM rate appreciably in either database. Because we included men with cT2NOS disease, cT1-T2a could not be used as a criterion for low risk.

We defined NCIM as no active treatment within 1 year of diagnosis. This method could not discriminate official active surveillance programs from watchful waiting. A recent SEER-Medicare study showed that in an elderly American population watchful waiting accounted for 87% of patients undergoing observation. In that study older age and higher tumor risk were associated with an increased use of watchful waiting. Thus, our finding that older age increased the odds of NCIM may have been due to greater use of watchful waiting, especially in men with intermediate risk PCs. Finally, in patients who underwent radical prostatectomy only pathological Gleason grade was available for analysis. Because of the high incidence of Gleason upgrading after surgery, this limitation likely removed some patients treated with surgery from our study or elevated others from low to intermediate risk PCs.

CONCLUSIONS
Using 2 independently managed cancer databases we determined that NCIM use increased greatly in patients with low risk PCs while the overall proportion of men who met low risk criteria decreased due to Gleason grade migration. Thus, overall NCIM use has not changed appreciably.

REFERENCES

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