# Contemporary Incidence and Outcomes of Prostate Cancer Lymph Node Metastases

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**Abbreviations and Acronyms**

PCSM = prostate cancer specific mortality

PLNM = pelvic lymph node metastases

SEER = Surveillance, Epidemiology and End Results

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**Purpose:** The incidence of localized prostate cancer has decreased with shifts in prostate cancer screening. While recent population based studies demonstrated a stable incidence of locoregional prostate cancer, they categorized organ confined, extraprostatic and lymph node positive disease together. However, to our knowledge the contemporary incidence of prostate cancer with pelvic lymph node metastases remains unknown.

**Materials and Methods:** We used SEER (Surveillance, Epidemiology and End Results) data from 2004 to 2014 to identify men diagnosed with prostate cancer. We analyzed trends in the age standardized prostate cancer incidence by stage. The impact of disease extent on mortality was assessed by adjusted Cox proportional hazard analysis.

**Results:** During the study period the annual incidence of nonmetastatic prostate cancer decreased from 5,119.1 to 2,931.9 per million men (IR 0.57, 95% CI 0.56–0.58, $p < 0.01$) while the incidence of pelvic lymph node metastases increased from 54.1 to 79.5 per million men (IR 1.47, 95% CI 1.33–1.62, $p < 0.01$). The incidence of distant metastases in men 75 years old or older reached a nadir in 2011 compared to 2004 (IR 0.81, 95% CI 0.74–0.90, $p < 0.01$) and it increased in 2012 compared to 2011 (IR 1.13, 95% CI 1.02–1.24, $p < 0.05$). The risk of cancer specific mortality significantly increased in men diagnosed with pelvic lymph node metastases (HR 4.5, 95% CI 4.2–4.9, $p < 0.01$) and distant metastases (HR 21.9, 95% CI 21.2–22.7, $p < 0.01$) compared to men with nonmetastatic disease.

**Conclusions:** The incidence of pelvic lymph node metastases is increasing coincident with a decline in the detection of localized disease. Whether this portends an increase in the burden of advanced disease or simply reflects decreased lead time remains unclear. However, this should be monitored closely as the increase in N1 disease reflects an increase in incurable prostate cancer at diagnosis.

**Key Words:** prostatic neoplasms, neoplasm metastasis, SEER Program, practice guidelines as topic, mortality

THE last decade was characterized by major shifts in prostate cancer epidemiology.[1–4] The prostate cancer incidence decreased from 175 to 100/100,000 men from 2007 to 2014[5] with a decrease in the incidence of local/regional prostate cancer.[2,6,7] Concurrent with this trend we



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reported that the decrease in localized disease detection was accompanied by an increase in the incidence of distant metastases in men older than 75 years following a nadir in 2011.[6] Others confirmed these findings.[2]

Using SEER data we also found that the proportion of men with PLNM at radical prostatectomy is increasing.[6,8] However, this may be secondary to selection bias in the performance of radical prostatectomy for higher risk features as up to 50% of men with low risk features now elect active surveillance.[9]

In this study we used the most recent update of SEER through 2014 to examine temporal changes in the incidence of nonmetastatic disease, PLNM and distant metastases. In addition, we studied PCSM in men with nonmetastatic disease and pelvic lymph node metastases to determine the potential consequences of an increase in nonlocalized disease.

## METHODS

### Study Population

The SEER program of NCI (National Cancer Institute) captures a representative sample of 28% of the American population.[10] We identified 573,669 men 50 years old or older who were diagnosed with pathologically confirmed prostate cancer from 2004 to 2014 to examine the incidence by SEER Collaborative Stage with time. Only the 475,153 men with prostate cancer as the only malignancy were included in mortality analysis to avoid potential confounding due to competing cancer specific mortality. Additionally, men with missing stage and missing survival time were excluded, resulting in 443,000 men available for analysis. Incident prostate cancers were categorized into 3 groups by disease extent at diagnosis, including group 1—nonmetastatic disease (T1N0M0, T2N0M0, T3N0M0 and T4N0M0), 2—PLNM (N1M0) and 3—distant metastasis (M1).

### Independent Variables

Sociodemographic characteristics included age at diagnosis (50 to 74 or 75 years old or older), race/ethnicity (Caucasian, African American, Hispanic or other), diagnosis year (2004 to 2008 or 2009 to 2014) and United States Census region (Northeast, South, Midwest or West). Clinical characteristics included pathological stage (T1, T2, T3 or T4), N stage (N0 or N1),[2,7] M stage (M0 or M1) and Gleason score (6 or less, or 7 or greater).

### Outcomes and Statistical Analysis

We evaluated the yearly and quarterly age adjusted incidences of prostate cancer per million men standardized to the 2000 United States Census population with time. The quarterly incidence was assessed graphically and a linear model or a restricted cubic spline model was fitted based on the Akaike information criterion. A restricted cubic splines model was chosen to provide a flexible description of the nonlinear relationship when linearity was inappropriate.[11,12] In addition, IRRs by year were calculated to evaluate relative changes in incidence to the beginning of the study period in 2004 and between each consecutive year. To account for missing values in TNM stage the quarterly incidence was derived by applying the proportion of each disease stage to the total number of men diagnosed with prostate cancer.

Sensitivity analysis was done to impute missing values with the clinical range of each cancer group.[13–15] We performed a subanalysis to account for potential detection bias secondary to increasing performance of prostatectomy in patients at high risk. The proportion of patients with PLNM who did and did not undergo prostatectomy was assessed by the Cochran-Armitage trend test.

Among men who had only prostate cancer we compared demographic characteristics, overall mortality and PCSM among those diagnosed with nonmetastatic disease, PLNM and distant metastases. Differences were evaluated using the percent of event count, the chi-square test for categorical variables and means, and the Kruskal-Wallis test for continuous variables.

Kaplan-Meier curves were constructed to visualize unadjusted overall mortality and PCSM. Cox regression was used to determine the HR of PCSM adjusting for year of diagnosis, age at diagnosis, race/ethnicity, tumor grade and pathology findings. Men with missing survival time were excluded from survival analysis. Statistical

**Table 1.** *Standardized annual incidence of prostate cancer per 1,000,000 men stratified by age*

| Age | Metastasis | | |
|---|---|---|---|
| | None | Pelvic Lymph Node | Distant |
| All 50 or Greater: | | | |
| 2004 | 5,119.1 | 54.1 | 226.5 |
| 2005 | 4,770.7 | 52.9 | 222.9 |
| 2006 | 5,186.3 | 53.6 | 217.3 |
| 2007 | 5,361.4 | 61.7 | 213.5 |
| 2008 | 4,869.6 | 60.3 | 207.0 |
| 2009 | 4,724.9 | 60.7 | 204.3 |
| 2010 | 4,475.8 | 66.5 | 207.6 |
| 2011 | 4,412.0 | 65.2 | 206.9 |
| 2012 | 3,546.9 | 65.2 | 220.4 |
| 2013 | 3,309.6 | 71.0 | 230.7 |
| 2014 | 2,931.9 | 79.5 | 235.2 |
| 50—74: | | | |
| 2004 | 4,616.3 | 60.2 | 136.0 |
| 2005 | 4,314.1 | 59.6 | 142.2 |
| 2006 | 4,768.0 | 59.4 | 134.5 |
| 2007 | 4,990.1 | 66.3 | 129.2 |
| 2008 | 4,607.0 | 63.1 | 130.4 |
| 2009 | 4,565.7 | 64.3 | 134.2 |
| 2010 | 4,318.8 | 69.7 | 137.0 |
| 2011 | 4,280.4 | 65.9 | 139.7 |
| 2012 | 3,495.5 | 67.4 | 141.3 |
| 2013 | 3,263.8 | 72.0 | 148.2 |
| 2014 | 2,880.3 | 80.5 | 157.3 |
| 75 or Greater: | | | |
| 2004 | 6,918.4 | 32.2 | 550.2 |
| 2005 | 6,405.0 | 29.2 | 511.8 |
| 2006 | 6,683.6 | 32.5 | 513.8 |
| 2007 | 6,690.1 | 45.6 | 515.1 |
| 2008 | 5,809.5 | 50.2 | 481.1 |
| 2009 | 5,295.0 | 47.8 | 455.2 |
| 2010 | 5,037.8 | 54.8 | 460.4 |
| 2011 | 4,883.1 | 62.7 | 447.3 |
| 2012 | 3,730.7 | 57.3 | 503.3 |
| 2013 | 3,473.5 | 67.5 | 526.0 |
| 2014 | 3,116.7 | 75.9 | 514.2 |