The Risk of Distant Metastases and Cancer Specific Survival in Men with Serum Prostate Specific Antigen Values above 100 ng/ml

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Abbreviations and Acronyms

IPR = National Inpatient Register

NPCR = National Prostate Cancer Register

PSA = prostate specific antigen

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Purpose: Current EAU (European Association of Urology) guidelines state that prostate specific antigen 100 ng/ml or greater at diagnosis indicates metastatic disease. We examined the association of prostate specific antigen 100 ng/ml or greater at diagnosis with distant metastasis and prostate cancer specific survival.

Material and Methods: A total of 15,635 men with prostate cancer diagnosed between 1998 and 2009 who were identified in PCBaSe (Prostate Cancer Data Base Sweden 2.0) were included in a population based registry study. Prostate cancer specific survival was compared among 3 groups, including 1,879 men with prostate specific antigen 100 ng/ml or greater and negative imaging (M0), 5,642 with distant metastases on imaging (M1) and prostate specific antigen 100 ng/ml or greater, and 3,828 with M1 and prostate specific antigen less than 100 ng/ml. A fourth group consisted of 4,286 men with prostate specific antigen 100 ng/ml or greater who had not undergone imaging (Mx). The latter men were not included in the assessment of survival.

Results: Of 7,521 men with prostate specific antigen 100 ng/ml or greater who underwent imaging for staging 75% were classified with M1 disease. Only 59% of 3,527 men with prostate specific antigen 100 to 300 mg/ml had distant metastases on imaging. Five-year prostate cancer specific survival was 72% (95% CI 70–74) in men with prostate specific antigen 100 ng/ml or greater and M0, 24% (95% CI 23–25) in men with prostate specific antigen 100 ng/ml or greater and M1, and 39% (95% CI 37–40) in men with prostate specific antigen less than 100 ng/ml and M1.

Conclusions: A fourth of men with prostate specific antigen 100 ng/ml or greater did not have distant metastases. They had twofold to threefold higher 5-year survival than men with distant metastases on imaging. Our findings strongly suggest that using prostate specific antigen 100 ng/ml or greater as an indicator of metastatic disease should be reconsidered.

Key Words: prostatic neoplasms, adenocarcinoma, prostate-specific antigen, neoplasm metastasis, Sweden

In men with prostate cancer high serum PSA at diagnosis is generally regarded as a strong indicator of advanced disease with distant metastases and poor prognosis.[1,2] Similarly low PSA is considered to make the

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presence of metastasis unlikely.[3–5] The 2013 EAU prostate cancer guidelines state, "A pre-treatment serum PSA value greater than 100 ng/ml has been found to be the single most important indicator of metastatic disease, with a positive predictive value of 100%."[2]

However, studies of associations between high PSA, distant metastases and survival are sparse and have been based on fewer than 200 cases.[1,6–8] Furthermore, to our knowledge it remains unknown whether prostate cancer specific survival in men with PSA 100 ng/ml or greater without evidence of distant metastases is similar to survival in men with evidence of distant metastases on imaging.

To this end we investigated the likelihood of distant metastases in men with PSA 100 ng/ml or greater at diagnosis who were identified in a nationwide, population based registry. We also compared survival in men with 1) PSA 100 ng/ml or greater with negative imaging (M0), 2) PSA 100 ng/ml or greater and metastasis verified by imaging (M1) and 3) PSA less than 100 ng/ml and metastasis verified by imaging (M1).

MATERIALS AND METHODS

PCBaSe is a research database including men documented with a prostate cancer diagnosis in NPCR between 1998 and 2012 that has previously been described in detail.[9] Briefly using an individually unique personal identity number issued to all residents in Sweden PCBaSe was generated by record linkages between NPCR and several other population based registries, including IPR, the Cause of Death Register, LISA (Longitudinal Integration Database for Health Insurance and Labour Market Studies) and the Population Register.

NPCR includes information on newly diagnosed prostate cancers (of which greater than 98% are adenocarcinoma), mode of detection, date of diagnosis, TNM stage, PSA at diagnosis, planned initial treatment and Gleason score, the latter since 2000. If the presence of metastasis was not investigated by an imaging modality, until 2013 M stage was categorized as Mx. NPCR captures 98% of all incident prostate cancers compared to the Swedish National Cancer Register, to which reporting is mandated by law. During the study period Swedish clinical guidelines recommended bone scan only as imaging in patients at risk for distant metastasis, eg because of PSA greater than 20 ng/ml. However, imaging was optional if the result would not alter patient treatment.

IPR reached national coverage in 1987 and includes information on inpatient care from all hospitals in Sweden. Each record contains dates of hospital admission and discharge, surgical procedures and up to 8 discharge diagnoses coded according to ICD-9 or 10. The validity of IPR is high since more than 99% of all somatic discharges are recorded. A validation of IPR showed that 85% to 95% of all diagnoses in the IPR are valid.[10]

For study purposes information in IPR was used to assess the comorbidity burden according to the Charlson comorbidity index to characterize patient groups and enable adjustment of survival analysis for comorbid conditions. Information on cause of death was retrieved from the Cause of Death registry in which all deaths in Sweden are recorded with cause of death reported by the attending physician according to ICD. The proportion of deaths with missing information on cause of death is low and in 2013 it was estimated at 1.1% of all deaths.[11]

LISA is a registry that includes socioeconomic data such as occupation, marital status, annual family income and highest achieved educational level. The Population Register continuously updates the vital status and the address of all residents, allowing for censoring at death or emigration.[9]

The study population included all men identified in PCBaSe with a prostate cancer diagnosis between 1998 and 2009 that fulfilled any of 4 criteria, including 1) PSA 100 ng/ml or greater with negative imaging (M0), 2) PSA 100 ng/ml or greater with metastasis verified by imaging (M1), 3) PSA less than 100 ng/ml and imaging verified metastasis (M1), and 4) PSA 100 ng/ml or greater without any imaging (Mx). The latter group was not included in the survival assessment.

Survival time was calculated as time from diagnosis to death, emigration or December 31, 2011, whichever was first. Prostate cancer specific survival was calculated by viewing death from prostate cancer as the event of interest while censoring for death from other causes. Calculations of survival and HRs were made separately in the 3 groups using a flexible parametric model[12] with group indicator as a covariate that varied by time. Separate analyses were performed based on 3 Gleason categories (Gleason score 2-6, 7 and 8-10). Estimates were then adjusted by including age at diagnosis as a restricted cubic spline and the Charlson comorbidity index in the models. Median age at diagnosis and baseline distribution of the comorbidity index of the whole sample was used to calculate adjusted 2, 5 and 10-year prostate cancer specific survival for a range of PSA values at each M stage.

RESULTS

Of the 15,635 men with prostate cancer included in study 1,879 (12%) were in the PSA 100 ng/ml or greater plus M0 group, 5,642 (36%) were in the group PSA 100 ng/ml or greater plus M1 group, 3,828 (24%) were in the PSA less than 100 ng/ml plus M1 group and 4,286 (27%) were in the PSA 100 ng/ml or greater plus Mx group. The table lists clinical characteristics.

Between 1998 and 2009 the age standardized incidence decreased by almost 50% in the MI plus PSA 100 ng/ml or greater group (from 6.6 to 3.6/100,000) and in the M0 plus PSA 100 ng/ml group. The M0 plus PSA 100 ng/ml or greater group showed a decrease from 2.3 to 1.3 whereas the M1 plus PSA less than 100 ng/ml group showed a decrease from 4.0 to 2.7/100,000 or 25% (supplementary fig. 1, http://jurology.com/). This pattern reflects a sharp increase in the use of PSA testing.