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Prognostic significance and biopsy characteristics of prostate cancer with seminal vesicle invasion on radical prostatectomy: a nationwide population-based study

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Summary

The objective of this study was to evaluate the prognostic significance of seminal vesicle invasion (SVI, pT3b) compared with extraprostatic extension (EPE) alone (pT3a) after radical prostatectomy, and to correlate pre-operative biopsy pathology with SVI and EPE.

The National Prostate Cancer Register includes all prostate cancers diagnosed in Sweden. We analysed 4063 cases with stage category pT3a and 1371 cases with pT3b at radical prostatectomy between 2000 and 2012. Associations between pT3a and pT3b and progression were evaluated and adjusted for year, age, biopsy grade and s-PSA. Needle biopsy findings in these stages were compared.

Patients with pT3b ($n = 1371$) had a higher risk of death from prostate cancer (HR 2.3, 95% CI 1.5–3.3, $p < 0.001$) and death from any cause (HR 1.5, 95% CI 1.2–1.8, $p < 0.001$) than those with pT3a ($n = 4063$). They were also more likely to be treated with post-operative radiotherapy (HR 1.5, 95% CI 1.4–1.7, $p < 0.001$) or androgen deprivation therapy (HR 3.0, 95% CI 2.5–3.7, $p < 0.001$), indicating clinical progression. Yet, disease-specific survival of patients with stage pT3b was 94% after 6 years. Median cancer extent in pre-operative biopsies of pT3a and pT3b was 14 and 24 mm ($p < 0.001$), number of positive cores was four and five, ($p < 0.001$) and biopsy Gleason score was 8–10 in 11.6% and 27.3%, respectively ($p < 0.001$).

SVI of prostate cancer is associated with worse outcome after radical prostatectomy than EPE alone. However, few patients with SVI die within 6 years from surgery, suggesting that radical prostatectomy may be curative in locally advanced cancers.

Key words: Prostate cancer; pathology; seminal vesicle invasion; extraprostatic extension; prognosis; needle biopsy.

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INTRODUCTION

Extraprostatic extension (EPE) and seminal vesicle invasion (SVI) by prostate cancer are well-established indicators of adverse prognosis.[1,2] EPE and SVI are defining features of stage category pT3a and pT3b disease, respectively, and both are associated with increased risk of local recurrence and mortality when compared to organ-confined disease.[3] SVI is considered a more sinister finding than EPE alone[4–6] and only lymph node metastases are associated with less favourable clinical outcome in locally advanced prostate cancer.[3,7] In early prostatectomy series most patients with SVI experienced progression of disease,[8,9] while those with EPE alone had a higher probability of remaining free of disease progression.[1,7,10] Since the introduction of serum prostate specific antigen (s-PSA) testing, prostate cancer is often detected at earlier stages and fewer men have advanced stage at radical prostatectomy.[11,12] Accordingly, the incidence of pT3a and pT3b disease has decreased considerably over the last decades. Regardless of this, studies continue to demonstrate poor clinical outcome for patients diagnosed with SVI.[13]

Previously, patients with SVI were thought to have such a poor prognosis that they were ineligible for treatment with curative intent. However, in recent years selected patients with locally advanced disease have been sometimes recommended for surgery.[14] Recent studies have shown improved clinical outcome for patients with adverse risk factors, such as SVI, when treated with radical prostatectomy in combination with post-operative radiotherapy.[15,16] For optimised treatment planning, accurate prediction of advanced disease is crucial. Occasionally, SVI and EPE may be diagnosed morphologically when biopsied; however, failing this, the biopsy characteristics of pT3b tumours are poorly understood. The percentage of cancer in the biopsy cores and the number of positive biopsy cores have both been suggested as predictors of post-operative stage although results are conflicting.[17–19]

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In Sweden, 98% of prostate cancers diagnosed are reported to The National Prostate Cancer Registry (NPCR). For this study we analysed 31,415 cases reported to the Registry that were diagnosed between 2000 and 2012, with patients treated by radical prostatectomy. We did this to evaluate associations between pT3a and pT3b staging category and tumour progression. The main aim of this study was to examine the prognostic significance of the seminal vesicle component among tumours extending beyond the prostate in a large cohort in the s-PSA era and also to analyse findings in preoperative biopsies.

MATERIALS AND METHODS

Study population and data collection

By law, all newly diagnosed cancers in Sweden are reported to the Swedish Cancer Registry. In addition, 98% of all newly diagnosed prostate cancers are reported to the NPCR, which registers clinical and pathological features as well as primary treatment. For this study, histopathological and clinical data were retrieved on all men who were diagnosed with prostate cancer between 2000 and 2012 and who underwent radical prostatectomy as the primary treatment. Detailed needle biopsy data have been systematically reported to the NPCR since 2009.

We collected information on biopsy Gleason scores, the sum of total cancer length within all cores, number of positive biopsy cores and percentage of positive biopsy cores for all pathological stages.

Missing values were imputed using multiple imputation based on chained equations,[20] creating five imputation data sets. pT stage was imputed for true missing values as well as in cases of no distinction between pT3a and pT3b.

Outcome measurements

NPCR data were merged with information from the Swedish Cause of Death Registry and Prescribed Drug Registry and were utilised for outcome analysis. Data on androgen deprivation therapy (ADT) was collected from the Prescribed Drug Registry, which started in 2005. Using the date 1 January 2006 as study entry allowed for a 6-month run-in period, leaving this data left-truncated. Left truncation was not needed for other endpoints. Death from all causes, death from prostate cancer or the initiation of post-operative radiation therapy (RT) and/or ADT were used as endpoints. Clinical progression was estimated from treatment with ADT or RT. Progression-free survival was estimated with exclusion of events up to 0, 1 and 2 years after radical prostatectomy. Patients who received RT and/or ADT within 2 years after radical prostatectomy were excluded from further analysis as they may have been treated with adjuvant intention. The exact timing of adjuvant radiotherapy may vary but even when such therapy is given immediately after the patient has recovered from radical prostatectomy, it will extend up to 6 months.[16] The exclusion of men who received RT up to 2 years after radical prostatectomy was decided based on the estimates at 0, 1 and 2 years and chosen to make sure that no men with adjuvant RT be misclassified as clinical recurrence. The radiation dose was considered when cases were included in the study in order to exclude patients who received palliative RT.[21]

Data processing/statistical analysis

Cox regression models were used for time-to-event analyses of death from prostate cancer, death from any cause or clinical progression. Kaplan–Meier curves were generated from the mean of the imputation data sets to compare progression-free survival between patients with category pT3a and pT3b tumours. Progression-free survival of patients with pT3a and pT3b tumours was analysed for each year from 2000 to 2012 to evaluate any temporal change in clinical outcome. Mann–Whitney U test and chi square test were used to compare biopsy data from men with cancer of staging category pT3a and pT3b. p values of less than 0.05 were considered statistically significant. All statistical analyses were performed using the program R statistics (version R-3.3.0).

RESULTS

Between the years 2000 and 2012 inclusive, 31,415 men with prostate cancer and treated by radical prostatectomy were reported to the NPCR. A total of 4063 (12.9%) and 1371 (4.4%) cases were staging category pT3a and pT3b, respectively. In 1163 cases, distinction between pT3a and pT3b was not made when the data were entered into the NPCR and tumours were registered as pT3 only. There were in general more missing values between 2000 and 2007, which made it difficult to interpret the proportions of the pathological staging categories for those years.

The clinical features of pT3a and pT3b cancers are presented in Table 1. The prostatectomy specimen Gleason scores were higher in pT3b than in pT3a tumours. In particular, Gleason scores 2–6 were reported in 1001 (24.6%) pT3a tumours and in 103 (7.5%) pT3b tumours, while Gleason score 8–10 was seen in 455 (11.2%) and 438 (31.9%) tumours, respectively. Median s-PSA at diagnosis was 7.4 ng/mL in pT3a and 9.2 ng/mL in pT3b category patients. Of patients with pT3b tumours, 455 (33.2%) and 159 (11.6%) received adjuvant RT and ADT, respectively. Adjuvant therapy was seen less frequently among patients with pT3a tumours, with only 806 (19.8%) and 154 (3.8%) undergoing adjuvant RT and ADT, respectively.

When adjusted for year of diagnosis, age, biopsy grade and s-PSA, patients with pT3b cancers had a higher risk of death from prostate cancer [hazard ratio (HR) 2.3, 95% confidence interval (CI) 1.5–3.3, $p < 0.001$] and death from any cause (HR 1.5, 95% CI 1.2–1.8, $p < 0.001$) when compared to pT3a. pT3b category tumours were also more likely to be treated with post-operative RT (HR 1.5, 95% CI 1.4–1.7, $p < 0.001$) or ADT (HR 3.0, 95% CI 2.5–3.7, $p < 0.001$), when excluding patients who received adjuvant treatment. This implies a higher rate of clinical progression (Table 2).

The progression-free survivals of pT3a and pT3b tumours are shown in Supplementary Table 1 (Appendix A). Since the medical treatment registry was initiated in 2005, ADT patients in the tables are limited to those treated with radical prostatectomy from 2006. Progression-free survival was lower for pT3b tumours than for pT3a, at 2, 4 and 6 years for every year of diagnosis. After 6 years, disease-specific survival of patients with stage pT3a and pT3b was 98% and 94%, respectively. When evaluating progression-free survival of RT patients only, the ratios were more similar between pT3a and pT3b when compared to ADT. The proportion of patients with SVI who had received neither RT nor ADT after 6 years ranged between 36.6% and 50.8% for the reporting years of the study. Kaplan–Meier curves are illustrated in Fig. 1. Supplementary Fig. 1A,B (Appendix A) show event-free survival with exclusion of events up to 0, 1 and 2 years after radical prostatectomy. Supplementary Fig. 2A–C (Appendix A) show risk of progression and prostate cancer specific death with stratification according to surgical margin status and exclusion of patients who received treatment 0, 1 and 2 years post-operatively. There was a higher risk of prostate cancer specific death and ADT treatment in patients with stage pT3b and positive surgical margins. These patients also had a higher risk of receiving RT when including all post-operatively treated men (Supplementary Fig. 2A, Appendix A). However, when excluding men who underwent RT the first 2 years after surgery this risk disappeared (Supplementary Fig. 2C, Appendix A).

Patients with pT3b tumours had more cancer in preoperative biopsies, with a greater total length of cancer, greater number of positive cores and higher percentage of Gleason score 8–10 cancer (Table 3). Median cancer extent

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