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Prostate Cancer

The Role of Prostate-specific Antigen Persistence After Radical Prostatectomy for the Prediction of Clinical Progression and Cancer-specific Mortality in Node-positive Prostate Cancer Patients

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Abstract

Background: A complete biochemical response (BR) immediately after surgery could be considered an indicator of optimal cancer control after radical prostatectomy (RP).
Objective: To evaluate the prognostic value of early postoperative prostate-specific antigen (PSA) levels after RP in patients with lymph node invasion (LNI).
Design, setting, and participants: The study included 319 prostate cancer patients with LNI who were treated with RP and extended pelvic lymph node dissection (ePLND) at a single institution between 1998 and 2013. All men had complete clinical, pathologic, and follow-up data, including PSA value at 6 wk after surgery. Patients were divided into two groups according to PSA value at 6 wk after surgery: complete BR (PSA $<$0.1 ng/ml) and PSA persistence (PSA $\geq$0.1 ng/ml).
Outcome measurements and statistical analysis: Kaplan-Meier analyses were used to assess 8-yr clinical recurrence (CR) and cancer-specific mortality (CSM) rates according to PSA persistence after RP. Multivariable Cox regression analysis was used to test the association between PSA persistence and CR. Covariates consisted of pathologic Gleason score ($\leq$7 vs $\geq$8), number of positive nodes, surgical margins status (negative vs positive), and adjuvant therapies (none vs androgen deprivation therapy (ADT) vs adjuvant radiotherapy plus ADT). When we performed multivariable analyses assessing the association between PSA persistence and CSM pathologic Gleason score represented the only covariate due to the low number of events (n = 13).
Results and limitations: Overall, 83 patients (26%) had PSA persistence. Men with PSA persistence had higher 8-yr CR and CSM rates than those with complete BR (69% vs 12% and 16% vs 4.2%, respectively; all $p \leq 0.002$). This was confirmed in multivariable analyses, where PSA persistence at 6 wk after surgery was an independent predictor of both CR (hazard ratio [HR]: 8.3; 95% confidence interval [CI], 4.73–14.7; $p \leq 0.001$) and CSM (HR: 2.16; 95% CI, 1.63–2.86; $p \leq 0.001$). Pathologic stage lower than pT3a, biopsy and pathologic Gleason score $\geq$8, positive surgical margins, and three or more positive lymph nodes were significantly associated with PSA persistence (all $p \leq 0.04$). Our study is limited by its retrospective design.

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Conclusions: Early BR can be achieved in approximately 75% of men with LNI submitted to RP and ePLND. PSA assessment early after surgery has an important prognostic role in the prediction of CR and CSM in node-positive patients. A risk stratification of these patients based on PSA persistence could guide physicians to properly select patients who may benefit the most from timely multimodal treatments.
Patient summary: The risk of clinical recurrence and cancer-specific mortality is heterogeneous in patients with prostate cancer with lymph node invasion. Node-positive patients with complete biochemical response early after surgery share more favorable oncologic outcomes than those with PSA persistence. These results are important to plan the optimal postoperative patient management.

1. Introduction

Approximately 10% of patients with clinically localized prostate cancer (PCa) treated with radical prostatectomy (RP) and extended pelvic lymph node dissection (ePLND) have lymph node invasion (LNI) at final pathology [1,2]. Historically, node-positive patients were considered to be affected by systemic disease [3]. However, recent studies demonstrated that the risk of progression and death is heterogeneous in these men [4–6]. Indeed, the outcomes of surgically treated patients with LNI are not invariably poor [4,5,7,8]. Approximately 30% of them do not experience biochemical recurrence after RP and ePLND at long-term follow-up [9]. Different tools have been developed to predict the outcome of patients with LNI, based on clinical and pathologic parameters [10–12]. However, none of them included a major prognostic factor for disease progression and outcomes: biochemical response (BR) postsurgery defined as early prostate-specific antigen (PSA) assessment after RP. Indeed, PSA values at 6 wk after RP could be a proxy for residual disease burden or occult distant systemic disease [13,14]. This might have important implications in planning the optimal postoperative strategy with the aim of avoiding the use of *blind* adjuvant therapies in the case of undetectable PSA level after RP. Indeed, despite the evidence supporting the use of adjuvant androgen deprivation therapy (ADT) in patients with LNI [15], several studies have shown that these individuals are extremely heterogeneous, with different outcomes according to PCa features. Therefore, despite being supported by a high level of evidence, such a one-size-fits-all approach may be questionable in this patient group. This hypothesis would be true, however, only if a positive association between early PSA response after RP and cancer control outcomes is shown. Unfortunately, this is currently unknown in the setting of node positive PCa. To address this void, we assessed the prognostic value of early postoperative PSA levels in men with LNI treated with RP and ePLND. We hypothesized that patients with PSA persistence at 6 wk after RP might show adverse clinical outcomes. These men would be at higher risk for recurrence and death from PCa and might benefit from multimodal therapeutic approaches.

2. Materials and methods

2.1. Study population

Patients with PCa treated with RP between 1991 and 2013 at a single tertiary center were identified (n = 8932). All patients included in our cohort had clinically localized or locally advanced PCa. Selected patients with enlarged lymph nodes were treated with surgery according to the treating physicians' preference. No patients included in our study had preoperative evidence of distant metastases. At the time of RP, an anatomically defined ePLND was performed in all the patients with intermediate- and high-risk PCa and in selected individuals with low-risk disease, according to the treating physicians' clinical judgment. The ePLND template included the fibrofatty tissue along the external iliac vein, with the distal limits being the deep circumflex vein and the femoral canal. Proximally, ePLND was performed up to and including the bifurcation of the common iliac artery. All fibrofatty tissue within the obturator fossa was removed to completely skeletonize the obturator nerve. The lateral limit consisted of the pelvic sidewall, and the medial dissection limit was defined by perivesical fat [16]. The dissection of presacral lymph nodes was performed in selected cases, according to the surgeons' attitude and experience. Our analyses focused on men with node-positive PCa (n = 1004 [11%]). Of these, we excluded 218 patients with incomplete clinical and/or pathologic data (ie, pathologic stage, pathologic Gleason score, surgical margins status) and 60 patients with incomplete follow-up data. This resulted in a population of 726 patients. Among these, only men with available data on the first PSA level measured at 6 wk after surgery were included (n = 319).

2.2. Covariates and follow-up

All 319 patients had complete data, including pathologic stage, pathologic Gleason score, surgical margin status, number of nodes removed, number of positive nodes, status of adjuvant and salvage therapies, and PSA values measured at 6 wk after surgery. None of the patients included in the study received neoadjuvant hormonal therapies or postoperative treatments before the first PSA assessment. Adjuvant ADT consisted of hormone-deprivation therapy initiated within 90 d of RP. Adjuvant radiotherapy (aRT) was defined as local radiation delivered to the prostatic and seminal vesicle bed, including the pelvic region, within 90 d of RP. This treatment modality was typically administered to patients with adverse pathologic features (ie, positive surgical margins, pathologic Gleason score $\geq$8, and pathologic stage pT3a or higher) [17] according to the clinical judgment of the treating physician. Salvage radiotherapy was administered in case of pelvic relapse in the absence of documented concomitant systemic recurrence. Persistent postoperative PSA was defined as a PSA $\geq$0.1 ng/ml at 6 wk after RP [14,18–20]. Serum PSA was measured every 3 mo for the first year, biannually between the second and the fifth years after surgery, and annually thereafter.

Patients underwent follow-up visits every 3 mo during the first year after surgery and every 6 mo thereafter. Biochemical recurrence (BCR) was defined as two consecutive increases in PSA $\geq$0.2 ng/ml. Clinical recurrence (CR) was defined as positive imaging during follow-up after the onset of BCR. All patients with CR included in this study underwent imaging after BCR at our center. This consisted of bone scan and/or computed tomography (CT) and/or abdominal magnetic resonance imaging and/or 11C-choline positron emission tomography/CT scan.