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Original article

Head-to-head comparison of lymph node density and number of positive lymph nodes in stratifying the outcome of patients with lymph node-positive prostate cancer submitted to radical prostatectomy and extended lymph node dissection

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Abstract

Objective: The aim of this study was to compare the predictive ability of lymph node density (LND) and number of positive lymph nodes in patients with prostate cancer and lymph node invasion.

Materials and methods: We included 568 patients with lymph node invasion treated with radical prostatectomy and extended pelvic lymph node dissection between January 1990 and July 2011 at a single center. The Kaplan-Meier method and multivariable Cox regression models tested the association between the number of positive lymph nodes or LND and cancer-specific survival (CSS). The predictive accuracy of a baseline model was assessed using Harrell's concordance index and then compared with that of a model including either the number of positive nodes or LND.

Results: The median number of positive lymph nodes was 2, whereas the median LND was 11.1%. At 5, 8, and 10 years, CSS rates were 92.5%, 83.9%, and 82.8%, respectively. At multivariable analyses, number of positive lymph nodes and LND, considered as continuous variables, were independent predictors of CSS (all $P \leq 0.01$). A 30% LND cutoff was found to be highly predictive of CSS ($P = 0.004$), and a cutoff of 2 positive nodes was confirmed to be a strong predictor of CSS ($P = 0.02$). The number of positive nodes and LND similarly, continuous or dichotomized, increased the accuracy for CSS predictions (0.68–0.69 vs. 0.61 of baseline model). LND cutoff of 30% increased the discrimination the most (0.69; +0.083).

Conclusions: The number of positive lymph nodes and LND showed comparable discriminative power for long-term CSS predictions. A cutoff of 30% LND might be suggested for the selection of patients candidate for adjuvant systemic therapy, because it increased the model's discrimination the most.

Keywords: Prostate cancer; Pelvic lymph node dissection; Radical prostatectomy; Staging; Outcome

1. Introduction

The introduction of prostate-specific antigen (PSA) screening and the subsequent stage migration among patients with prostate cancer (CaP) have led to a drastic decrease in the incidence of lymph node metastases at the time of radical prostatectomy (RP) [1,2]. However, the rate of lymph node invasion (LNI) is not only dictated by clinical features of the disease, but also strongly related to the extent of pelvic lymph node dissection (PLND) [3–7]. In this context, a general agreement has been reached on the statement that whenever a PLND is indicated, it should be anatomically extended (ePLND) [8,9]. Such an accurate nodal staging is important, because not all patients with LNI share the same prognosis. Survival among node-positive

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patients has indeed been linked to the number of positive lymph nodes [3]. Several studies reported excellent cancer-specific survival (CSS) outcomes for patients with limited nodal involvement as compared to men with more extended nodal involvement [10–14]. Even in the absence of solid, prospective data, these patients might be spared from systemic therapy, assuming an undetectable PSA after surgery. However, the absolute number of positive nodes might lose its prognostic value when considering the total number of removed lymph nodes, thus leading to the concept of lymph node density (LND). In LND, the absolute number of nodal metastases is divided by the total number of removed lymph nodes. In bladder cancer, this ratio has shown to be superior to classical nodal staging in predicting long-term mortality [15,16]. Also, in some CaP series, LND has proven to better stratify long-term outcome [17–19]. However, no study to date has tested whether LND is superior to the number of metastatic nodes in stratifying patient survival. Indeed, as LND is a ratio, the value of 10% can be applied to a man with 1 positive node of 10, as well as to a patient with 3 metastases of 30 examined nodes. The aim of our study was to test whether LND is superior to the number of nodal metastases in predicting long-term CSS.

2. Materials and Methods

2.1. Patient population

After Institutional Review Board approval, we reviewed 779 consecutive lymph node-positive patients who underwent RP and anatomically defined ePLND for CaP at a single tertiary referral center between January 1990 and July 2011. Of these patients, 21 men were excluded due to lack of data on the number of total lymph nodes removed; 91 men were excluded due to incomplete follow-up data; and 99 patients without data on adjuvant therapies were excluded. This yielded to a final study population of 568 patients. No patient had evidence of distant metastatic disease at preoperative imaging, which included abdominopelvic computerized tomography, bone scan, and chest x-ray.

All men underwent an anatomically defined ePLND, as previously described [20], irrespective of their preoperative risk. The ePLND consisted of excision of fibrofatty tissue along the external iliac vein, with the distal limit, the deep circumflex vein, and the femoral canal. Proximally, the ePLND was performed up to and including the bifurcation of the common iliac artery. All fibrofatty tissue within the obturator fossa was removed to skeletonize the obturator nerve completely. The lateral limit consisted of the pelvic sidewall, and the medial dissection limit was defined by perivesical fat. Lymph nodes along the internal iliac artery were also removed. Surgeries were performed by 10 experienced surgeons. The nodal specimens were submitted for pathologic examination in multiple packages, in order to improve the quality of specimen assessment [21]. Fat tissue containing lymph nodes was fixed in 10% buffered formalin. For each anatomical group, the number of nodes, the size of the largest node, and any gross features were described. Macroscopic specimen assessment was based on tactile and visual criteria. Large nodes (>2 cm) were sampled in multiple blocks. If no lymph nodes were macroscopically detected, all fat tissue was processed. Clearing solution was generally not used for pelvic lymph nodes. All blocks were embedded in paraffin, cut at 3 μm, and stained with hematoxylin-eosin. In selected cases, immunohistochemical stain for cytokeratin and multiple sections was analyzed. All men had complete clinical and pathologic data. It included age at surgery, preoperative PSA, pathologic stage defined according to the 2002 American Joint Committee on Cancer staging system [22], pathologic Gleason score, surgical margin, and adjuvant treatment status. Moreover, detailed data on the number of lymph nodes removed and on the number of positive lymph nodes were available. LND was defined as the ratio between the number of positive lymph nodes and the total number of lymph nodes removed.

2.2. Adjuvant therapies

Overall, 73% of the patients ($n = 417$) received adjuvant hormonal therapy (HT) and 70% of the men ($n = 398$) underwent adjuvant radiation therapy administered within 90 days after RP.

In detail, 306 patients received both forms of adjuvant treatment, whereas 59 did not undergo any further therapy after RP. The decision to administer 1 or both forms of adjuvant treatments followed the surgeon and patient discussion on possible treatment options. Medical hormone deprivation therapy was generally intended to be lifelong. However, given the retrospective nature of this study, it is uncertain whether patients discontinued treatment after a period of HT. With respect to radiotherapy field, 107 patients (27%) underwent irradiation of the prostatic bed only, whereas the remaining 291 patients (73%) underwent irradiation of the pelvis.

2.3. Statistical analysis

The statistical approach consisted of 3 different steps. First, the Kaplan-Meier method was used to graphically explore CSS in the overall population as well as after stratification according to the number of positive lymph nodes and LND. The cutoff used for the number of positive lymph nodes was 2 [12], whereas LND was dichotomized according to the most informative cutoff. The latter was obtained by applying analysis of variance test for every possible cutoff value and choosing the lowest P-value, as previously described [12]. Differences in survival were tested with the log-rank test. Second, univariable and multivariable Cox regression analyses were performed to