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Marked Prognostic Impact of Minimal Lymphatic Tumor Spread in Prostate Cancer

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Abstract

Background: Nodal metastasis (N1) is a strong prognostic parameter in prostate cancer; however, lymph node evaluation is always incomplete.
Objective: To study the prognostic value of lymphatic invasion (L1) and whether it might complement or even replace lymph node analysis in clinical practice.
Design, setting, and participants: Retrospective analysis of pathological and clinical data from 14 528 consecutive patients.
Intervention: Radical prostatectomy.
Outcome measurements and statistical analysis: The impact of L1 and N1 on patient prognosis was measured with time to biochemical recurrence as the primary endpoint.
Results and limitations: Nodal metastases were found in 1602 (12%) of 13 070 patients with lymph node dissection. L1 was seen in 2027 of 14 528 patients (14%) for whom lymphatic vessels had been visualized by immunohistochemistry. N1 and L1 continuously increased with unfavorable Gleason grade, advanced pT stage, and preoperative prostate-specific antigen (PSA) values ($p < 0.0001$ each). N1 was found in 4.3% of 12 501 L0 and in 41% of 2027 L1 carcinomas ($p < 0.0001$). L1 was seen in 11% of 9868 N0 and in 61% of 1360 N1 carcinomas ($p < 0.0001$). Both N1 and L1 were linked to PSA recurrence ($p < 0.0001$ each). This was also true for 17 patients with isolated tumor cells (ie, <200 unequivocal cancer cells without invasive growth) and 193 metastases ≤1 mm. Combined analysis of N and L status showed that L1 had no prognostic effect in N1 patients but L1 was strikingly linked to PSA recurrence in N0 patients. N0L1 patients showed a similar outcome as N1 patients.
Conclusions: Analysis of lymphatic invasion provides comparable prognostic information than lymph node analysis. Even minimal involvement of the lymphatic system has pivotal prognostic impact in prostate cancer. Thus, a thorough search for lymphatic involvement helps to identify more patients with an increased risk for disease recurrence.
Patient summary: Already minimal amounts of tumor cells inside the lymph nodes or intraprostatic lymphatic vessels have a severe impact on patient prognosis.

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1. Introduction

Finding tumor cells in a lymph node is unequivocal proof for cancer dissemination and usually implies adjuvant systemic therapy if adequate treatment options are available [1–6]. In prostate cancer, adjuvant systemic therapy after primary surgery is recommended as androgen deprivation therapy in patients with lymph node positive (pN1) tumors [7]. Over the past few years, the number of novel systemic therapies available for metastatic and castration-resistant prostate cancer has greatly increased [8–12], and the use of these drugs in pN1 patients without distant (bone or visceral) metastases is increasingly analyzed in studies [13,14].

Thus, accurate assessment of lymph node involvement is of increasing importance after prostatectomy. Today, histopathological assessment of surgically removed lymph nodes is the only accepted staging method to define a pN+ prostate cancer status. However, nodal status assessment in prostate cancer is not standardized. Complete resection of potentially involved lymph nodes is not feasible due to morbidity caused by overly extensive surgery. A discernible sentinel node, where the first metastasis is expected to locate, does not exist [15]. The quantity of removed lymph nodes varies greatly between surgeons [16,17]. The histopathological work-up of lymph node-containing tissue also varies between laboratories. Inconsistencies here include the embedding of palpable nodes versus embedding the entire fat tissue, cutting one versus multiple sections per lymph node, as well as the use of immunohistochemistry (IHC) or other auxiliary methods for metastasis detection [18].

A less invasive surrogate for measuring a tumor's capability to metastasize to lymph nodes is thus highly desirable. In theory, an accurate assessment of the lymphatic vessel status should mirror the situation in the lymph nodes. Intraprostatic lymphatic vessel infiltration by the tumor has been discussed as a prognostic feature in prostate cancer [19,20]. Several studies have also shown a strong link between lymphatic vessel invasion and positive lymph nodes [19,21].

The current study was undertaken to evaluate the prognostic value of a thorough lymphatic vessel analysis and whether it can complement or even replace the information on a cancer's lymphogenic metastatic potential to an extent that regional lymph node examination could be reduced or omitted. Over the past 10 yr, we have systematically improved our protocols for the detection of lymph nodes and systematically analyzed lymphatic vessel infiltration in prostatectomy specimen. Here we report on the combined impact of lymphatic vessel and nodal status in a cohort of more than 11 000 patients.

2. Material and methods

2.1. Patients

Radical prostatectomy specimens were available from 17 987 consecutive patients, undergoing surgery between 2005 and 2015 at the Department of Urology and the Martini-Klinik, Prostate Cancer Center at the University Medical Center Hamburg-Eppendorf, Germany. Immunohistochemical lymph vessel invasion analysis had been performed in 14 528 of the 17 987 patients. The nodal status was N0 in 9868, N1 in 1360, and Nx in 3300 of these 14 528 patients. A total of 13 070 patients underwent lymph node dissection. Detailed data on the number of retrieved lymph nodes was recorded from 11 799 patients. Follow-up data were available from 15 032 patients (including 10 697 patients who underwent lymph node dissection and 12 059 patients with immunohistochemical lymph vessel invasion analysis) from the Martini-Klinik database (H. Huland) with yearly patient reported outcome measurement and a typical annual follow-up rate of more than 90%. There was a median follow-up of 36 mo (25% quartile: 14 mo, 75% quartile: 60 mo). In total, 1127 patients received neoadjuvant and/or adjuvant hormone therapy. These patients were excluded from outcome analyses as such treatment may obscure prostate-specific antigen (PSA) recurrence, which was used as the study endpoint in our prognosis analyses. PSA values were measured following surgery, and PSA recurrence was defined as a postoperative PSA $\geq$0.2 ng/ml confirmed by a second analysis with a serum PSA $\geq$0.2 ng/ml. All prostate specimens were analyzed according to a standard procedure, including complete embedding of the entire prostate for histological analysis. An overview of the analyzed patient cohort is given in Table 1 and Supplementary Figure 1.

2.2. Lymph node analysis

The method for lymph node preparation (done by pathologists) changed over time. From January 2005 to November 2008, only palpable lymph nodes were histologically analyzed. From November 2008 to November 2012, the remaining fat tissue without macroscopically distinguishable nodes was also paraffin embedded and histologically analyzed. From November 2012 to June 2014, at least four lymph node-containing tissue blocks, mostly those with particularly large nodes, were selected by pathologists to be additionally analyzed by IHC using the pan-epithelial antibody AE1/3, known to stain virtually all prostate cancer cells. Since June 2014, the fat tissue was always pretreated with acetone to make it less slippery and to facilitate palpation. Since September 2014, at least eight lymph node-containing tissue blocks are always analyzed by IHC (AE1/3). This expansion was because we were increasingly worried by a number of very small metastases found in very small lymph nodes (<5 mm) that were usually not analyzed by IHC before. For the purpose of IHC, freshly cut sections were deparaffinized and exposed to heat-induced antigen retrieval for 5 min in an autoclave at 121 °C in pH 7.8 Tris-EDTA-citrate buffer. A primary antibody specific for AE1/3 (rabbit polyclonal antibody; Sigma-Aldrich, St. Louis, MO, USA; cat#HPA037888; dilution 1:150) was applied at 37 °C for 60 min. The bound antibody was then visualized using the EnVision Kit (Dako, Glostrup, Denmark) according to the manufacturer's directions. All nodal metastases were reviewed and measured for the purpose of this study.

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