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Description and clinicopathological relevance of Lymphangiogenesis in invasive transitional cell carcinoma of the bladder: a potential prognostic factor?

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About 30% of bladder transitional cell carcinomas (TCC) present as muscle-invasive disease. Once TCC metastasizes the prognosis is poor with a long-term survival of less than 10%. Analysis of several characteristics of bladder TCC, including pathologic features and molecular markers, have failed to provide robust predictive markers of the disease course. Lymphatic vasculature within or in proximity to tumors serve as the primary conduit for metastatic spread. Discovery of lymphatic endothelial cell (LEC) markers and cytokines stimulating LECs have focused attention on lymphangiogenesis. The newly developed D2-40 antibody can be specifically used for identification and quantification of lymph vessels in immunohistochemical studies. The potential role of lymph vessel density as a prognostic factor as well as the functional significance of tumoral lymph vessels has not been investigated in invasive bladder TCC so far. The aim of the study was to describe and evaluate the association of lymphatics with clinicopathological parameters and disease-specific survival. Furthermore, proliferation of LEC's was evaluated in order to assess the functional significance of tumoral lymph vessels.

Information of 108 patients with histopathologically defined muscle-invasive TCC of the bladder who underwent radical cystectomy in the Department of Urology of the University Hospital Mannheim from 1998 to 2005 were reviewed retrospectively. Complete follow-up data existed for 103 patients (95,4%) and ranged from 1 to 90 months (mean 26,8). Sections were analyzed immunohistochemically for D2-40. Counts of lymph vessels were performed in 3 areas: intratumoral (ITLVD), peritumoral (PTLVD) and in normal tissue (NTLVD). In order to detect proliferating LECs, a double immunostaining for D2-40 and Ki-67 (clone MIB-1) was performed. Expression of the Ki-67 antibody in the nucleus of LECs was considered as sign of proliferation. Doublestaining with the endothelial marker CD-34 antibody and D2-40 was performed for simultaneous visualization of blood and lymph vessels.

Arrangement of several lymph vessels in the surrounding area of the tumor was observed in 105 sections (97,2%). Identification of intratumoral vessels was possible in 65 sections (60,2%). These vessels were smaller and less numerous than those in the peritumoral area. Doublestaining clearly distinguished D2-40-positive lymphatic vessels from neighboring D2-40-negative blood vessels, which in turn were stained by CD-34 and contained erythrocytes. LVD in the peritumoral regions was significantly higher than in the intratumoral areas as well as than in normal tissue. Higher ITLVD correlated significantly with poor histological differentiation. There was no significant association with pathological stage or lymph node status. Higher PTLVD showed a weak association with higher histological grade and a significant association with the presence of lymph node metastasis. PTLVD showed no influence on pathological stage. A significant association was observed between higher NTLVD and lymphatic metastasis. Univariate analysis showed that a higher pathological T stage, a poorer histological grade and the presence of lymph node metastasis were the only significant prognostic factors for reduced disease-specific survival. Lymph vessel densities showed no statistically significant influence on survival. Intratumoral and peritumoral vessels showed cycling endothelial cells in all examined samples in a variable proportion.

Lymphangiogenesis occurs in muscle-invasive bladder TCC. To our knowledge, the current study is the first to investigate and confirm a strong correlation of higher PTLVD with presence of positive lymph nodes in clinically localized bladder TCC. According to these results, an increased PTLVD may facilitate dissemination to locoregional lymph nodes. In contrast, intratumoral vessels are probably not major routes for nodal dissemination. The present study is also the first to suggest the existence of proliferating lymph vessels in bladder TCC. Further studies will have to determine if this information will contribute to improve outcomes of this malignancy.