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Etiologic, Diagnostic and Prognostic factors in Vulvar Cancer

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ABSTRACT

Vulvar Squamous Cell Carcinoma (VSCC) can be divided into two subgroups basaloid and/or warty (HPV-associated) and keratinizing/non-keratinizing carcinomas (not HPV-associated).

The inguinal lymph node status represents the most powerful prognostic factor. The Sentinel Node (SN) procedure is an alternative to complete inguinofemoral lymphadenectomy, which diminishes the complications. In this thesis the value of preoperative lymphoscintigraphy and the SN procedure was assessed. It was discovered that the relation between SNs detected on the scintigram and those found during surgery showed good agreement using Weighted Kappa. The detection rate of SN was 98% for radioisotope plus blue dye, and 94% for blue dye alone. The false negative rate was 2.7%.

Hr-HPV (16, 18, 33, or 52) was detected in 31% of the tumours and in 43% of the SNs in patients with HPV-positive tumours. Patients with HPV-positive VSCC were significantly younger at diagnosis and had better survival. SNs with metastases were more frequently HPV-positive than those without metastases.

As in many other cancer forms, there is a need for new and better prognostic markers in vulvar cancers. High expression of ln-5γ2 chain and HPV negativity were associated with poor outcome. In a multivariate analysis only HPV status and tumour stage were significant factors for survival. Ln-5γ2 expression showed positively significant correlation with stage, tumour-size, grade and metastases, but was negatively associated with HPV status. Expression of the proliferation marker Ki-67 was significantly correlated with HPV status.

Studies of the proteome characteristics of HPV- positive versus HPV-negative VSCC by protein and pathway profiling on a global and individual tumour level detected four proteins as playing a major role in discriminating relapse from non-relapse tumours: STAT1, MX1, LGMN and PSMA5. Validation by immunohistochemistry showed significant down-regulation in HPV-positive compared to HPV-negative tumours. In the individual tumour pathway analysis, the pathways "RIG-1 like receptors in antiviral innate immunity" and "Rac signalling" emerge discriminate for separating relapse from non-relapse.

In conclusion; preoperative scintigram gives the best estimate of the accurate number of lymph nodes but cannot determine if unilateral or bilateral groins should be explored in cases of midline tumours. Presence of HPV DNA in SN was related to metastatic disease but did not affect survival.

High expression of ln-5y2 chain and HPV negativity were associated with poor outcome. However in multivariate analysis only HPV status and FIGO-stage showed significant relation to survival. Alterations of the "RIG-1 like receptors in antiviral innate immunity" pathway may be linked to an unfavourable prognosis, while alterations of the "IFN/EGFR/Glucocorticoid" signalling pathway is associated with HPV-positive tumours and thus of favourable prognosis.