


 PENILE CANCER

Ongoing search for molecular prognostic markers

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Two studies propose new possible prognostic markers for men with penile squamous cell carcinoma (PSCC). One found that increased expression of insulin-like growth factor 1 receptor (IGF1R) is associated with disease progression and decreased progression-free survival (PFS). The other identified decreased expression levels of three specific microRNAs (miRNAs) in metastatic tumours and decreased survival in patients with this expression signature.

Penile cancer is one of the rarer urological malignancies and patient survival is high when the disease is diagnosed early and has not spread to neighbouring lymph nodes. However, in men with nodal metastases, survival is considerably decreased, particularly in those in whom pelvic lymph nodes are involved. Inguinal lymph node dissection is performed in some patients with cN0 disease and markers that could predict the presence of micrometastatic disease might avoid unnecessary procedures that have a high risk of complications. To date, several potential molecular markers to predict disease progression have been investigated but no marker has entered routine clinical practice.

Two new studies that further explore possible prognostic markers have now been published: the first used immunohistochemical assessment of protein expression levels and the second investigated miRNA expression levels in biopsy samples of nonmetastatic and metastatic tumours.

Mark Ball and colleagues from The Johns Hopkins University School of Medicine in Baltimore, USA, queried their archive and database of tissues from patients with PSCC. Tissue microarrays of primary tumour tissues from 53 men were stained for IGF1R expression and assessed according to a four-tier scoring system. IGF1R is involved in cell proliferation and transformation and overexpression has been detected in several types of cancers. Samples from 33 patients (62%) were positive for IGF1R expression. Increased expression levels were, for example, associated with lymphovascular and perineural invasion. At a median follow-up period of 27.8 months, 16 patients who had

increased IGF1R expression, but only 2 patients without IGF1R overexpression, had progressed ($P=0.006$). In addition, men with increased IGF1R expression levels had decreased PFS ($P=0.003$). Multivariate analysis adjusted for pathological features showed that IGF1R overexpression was an independent prognostic factor (HR 2.3, 95% CI 1.1–5.1; $P=0.03$).

The second study on miRNA expression in PSCC was performed by Juliane Hartz and team from the Rostock University Medical Center, Germany. The researchers analysed samples of primary tumours and, if applicable, synchronous inguinal lymph node metastases from 24 patients. They found that expression levels of miR-1, miR-101 and miR-204 were significantly lower in primary tumours of men who had lymph node metastases, as well as in the metastatic tissues themselves, compared with those with nonmetastatic disease ($P<0.05$). Log-rank analysis showed that the combined decrease of the three miRNAs correlated with patient survival (HR 0.078; $P=0.0315$). Evaluating functional relevance, the team determined 189 genes linked to these miRNAs and comparison with online-available microarray datasets showed that several of these genes that are overexpressed have been implicated in metastasis in men with PSCC.

Small sample sizes are a limitation of most studies of PSCC and large prospective studies are needed to determine the usability of prognostic markers in this disease. However, lymph node involvement is the pre-eminent prognostic factor of patient survival and the availability of clinically reliable molecular markers might help to minimize the need for invasive lymph node staging and the resulting complications.

Clemens Thoma

ORIGINAL ARTICLES Ball, M. W. et al. Overexpression of insulin-like growth factor-1 receptor is associated with penile cancer progression. *Urology* <http://dx.doi.org/10.1016/j.jurology.2016.02.006> (2016) | Hartz, J. M. et al. Integrated loss of miR-1/-101/-204 discriminates metastatic from non-metastatic penile carcinomas and can predict patient outcome. *J. Urol.* <http://dx.doi.org/10.1016/j.juro.2016.01.115> (2016)

FURTHER READING Shabbir, M. et al. Challenges and controversies in the management of penile cancer. *Nat. Rev. Urol.* **11**, 702–711 (2014)