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Introduction & Objectives: Radical resection of lymph node (LN) metastases improves oncologic outcome in muscle invasive bladder cancer (MIBC) and can even cure patients with node positive disease of penile cancer. New targeted bio-optical imaging modalities using tumor-directed monoclonal antibodies may be of value to improve the intraoperative detection and resection of LN metastatic disease.

The current study evaluates the expression of EpCAM, PSMA and VEGF in primary tumors and LN metastases compared to LNs without metastases in urothelial cell carcinoma (UCC) of the bladder and squamous cell carcinoma (SCC) of the penis. We compared the expression of these antibodies with the expression of the clinically used antibody Pan-Cytokeratin (CK AE1/AE3).

Materials & Methods: LN metastases and matched LNs without metastases of patients who underwent LN dissection because of MIBC and penile cancer were used. Primary tumors of the same patients were used from (partial) penectomy specimen and cystectomy specimen, transurethral resections and/or biopsies. Immunohistochemistry was performed to determine antigen expression. The Total Immunostaining Score (TIS, 0-12) was determined as the product of a Proportion Score (PS, 0-4) and an Intensity Score (IS, 0-3).

Results: Median TIS (interquartile range, IQR) of all antibodies is presented in Table 1. High Pan-Cytokeratin expression was seen in all primary tumors and LN metastases of UCC and SCC. VEGF expression was high in primary tumor and LN metastases, especially in LN metastases of SCC. However VEGF expression was also presented in LNs without metastases. Tumor-to-background ratio of VEGF expression in LNs was 2.6 in SCC and 1.3 in UCC. EpCAM expression was observed in primary tumors and LN metastases of UCC, but not in LNs without metastases. No EpCAM expression was seen in SCC at all. Mild PSMA expression was seen in endothelial cells surrounding tumor tissue. However, no PSMA

expression was seen in epithelial tumor tissue itself.

Table 1. Scoring immunoreactivity of all antibodies

	CK AE1/AE3		VEGF		PSMA		EpCAM	
	<i>n</i>	TIS (IQR)	<i>n</i>	TIS (IQR)	<i>n</i>	TIS (IQR)	<i>n</i>	TIS (IQR)
Primary SCC penis	22	12 (12-12)	22	7 (6-8)	5	0 (0-2)	5	0 (0-0)
LN+ SCC penis	25	12 (12-12)	25	8 (5-8)	5	2 (1-2)	5	0 (0-0)
LN-			22	3 (2-3)				
Primary UCC bladder	17	12 (12-12)	17	8 (4-8)	12	2 (0.3-2)	12	6 (2.3-11)
LN+ UCC bladder	23	12 (12-12)	23	4 (3-8)	13	2 (0.5-2)	20	5 (2-8)
LN-			17	3 (2.5-3)			14	0 (0)

TIS: Total Immunostaining Score, IQR: interquartile range

Conclusions: This study shows that VEGF has a high expression in LN metastases of SCC of the penis. EpCAM has a high expression in LN metastases of UCC of the bladder. Based on this study, VEGF and EpCAM need further evaluation to determine its valuability as a target for imaging modalities to assess LN metastases of MIBC and penile cancer.