

## Transitional cell carcinoma of suspected ureteral origin, with intra-abdominal and distant metastases in two horses

### *Overgangscelcarcinoom vermoedelijk uitgaande van de ureter, met uitgebreide metastasering bij twee paarden*

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#### ABSTRACT

The present paper describes two cases of suspected urothelial carcinomas with local lymphatic metastases, and distant metastases in the lungs. In one case, liver metastases were also present. Both cases are documented with an extensive clinical report, using bloodwork, rectal examination, ultrasonography, cytology of abdominal fluid and, in one case, also urine analysis, radiography and transrectal biopsy to come to a diagnosis of abdominal malignancy. Subsequently, the post-mortem exam, histopathology and immunohistochemistry are described and illustrated.

#### SAMENVATTING

In dit artikel worden twee gevallen beschreven van overgangscelcarcinomen vermoedelijk uitgaande van de ureter, met metastasen via de regionale lymfevaten en met longmetastasen. In één geval waren er ook levermetastasen. Het klinisch onderzoek komt uitgebreid aan bod, met een bespreking van onder andere het bloedonderzoek, rectaal onderzoek, de echografie en de cytologie van buikvocht. In één van de twee gevallen worden eveneens het urineonderzoek, de radiografie en transrectale biopsname besproken en wordt een maligne abdominaal proces gediagnosticeerd. Daarna wordt het pathologisch onderzoek beschreven en verduidelijkt met illustraties.

#### INTRODUCTION

Primary neoplasms of the equine urinary tract are uncommon (Traub-Dargatz, 1998). Published cases document mainly malignant epithelial tumors of the kidney and urinary bladder (Patterson-Kane *et al.*, 2000). Renal carcinoma (or renal adenocarcinoma) is the most common form of primary upper urinary tract neoplasia in horses (Berggren, 1980; Servantie *et al.*, 1986; Rhind *et al.*, 1999; Rumbaugh *et al.*, 2003; Wise *et al.*, 2009). Renal carcinoma can be locally invasive and/or metastasize to various organs. Therefore, the prognosis is generally poor (Wise *et al.*, 2009). Urothelial or transitional cell carcinomas (TCC) arising in the ureter have been infrequently reported in dogs after the administration of chemical carcinogens (Haneka and Rebar, 1953; Scott and Boyd, 1980). In humans, transitional cell neoplasia of the renal pelvis and ureter is well documented and classified (AJCC, 2006). To the author's knowledge, tumors of the renal pelvis or ureters have not previously been reported in horses. This report describes two cases of metastatic transitional cell carcinoma presumably originating from the ureter.

#### CASE DETAILS

##### Case 1

##### History

A 20-year-old 509 kg French Warmblood mare was presented at the Department of Large Animal Internal Medicine, Ghent University, with a history of weight loss and partial anorexia for 5 weeks. The last week, the horse had been suffering from ventral edema. On clinical examination, the horse had a body score of 2/9 (Henneke Body Condition Scoring System), a body temperature of 38.5°C, a heart rate of 36/min and a respiratory rate of 20/min. The packed cell volume was 36% (ref. values: 32-53%), with a red blood cell count of 5.5 X10<sup>12</sup>/l (ref. values: 6.7-12.9 X 10<sup>6</sup>/l) and hemoglobin concentration of 100 g/l (ref. values: 110-190 g/l). The total white blood cell count and differentiation were normal. The biochemical blood analysis remained within normal limits, except that the lactate dehydrogenase (421 IU/L) (ref. value: 162-412 IU/L) and the gamma-globulin fraction (2.5 g/dl) (ref. values: 0.55-1.9 g/dl) were mildly elevated. The thoracic sounds

were slightly increased and the abdominal sounds were normal. The rectal examination was normal. Urine analysis was not performed. On gastroscopic examination, pronounced ulcerations (grade 4/4) along the margo plicatus were present. Transthoracic ultrasonography showed comet tails on both sides. Transabdominal ultrasonography revealed the presence of a large amount of free fluid. On abdominocentesis, a clear, yellow peritoneal fluid with a total protein of 11 g/l and a white blood cell count of  $1.1 \times 10^9/l$  was collected. Cytology of the fluid showed a moderately cell rich smear on a background of red blood cells and numerous atypical cells. In a period of 5 days, the horse had lost 43 kg of weight. This, together with the atypical cells found on abdominal fluid cytology, gave rise to a suspicion of malignancy. Because of the bad prognosis, it was decided to euthanize the horse.

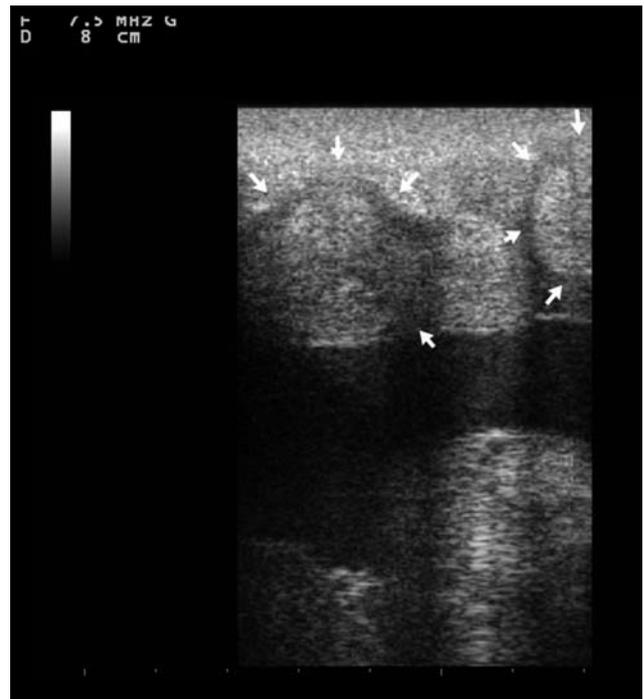
### *Necropsy findings*

At necropsy, the horse was cachectic with severe ventral subcutaneous edema and ascites. Multiple (20 to 30) well circumscribed round, non-encapsulated, pale tan, 2 to 15 cm diameter masses were present along the entire length of the abdominal aorta. Transverse sections of the nodules revealed multifocal hemorrhage and necrosis. The largest mass (15 cm diameter) was retroperitoneally caudoventral to the right kidney, surrounding the most proximal 15 cm of the ipsilateral ureter. The ureteral mucosa at this site showed no grossly visible alteration. There was no connection between the masses and the kidneys or other parts of the urinary tract. Numerous small (0.5 to 1 cm diameter) masses with similar macroscopic characteristics were scattered within the lung parenchyma. The gastric mucosa was severely ulcerated.

## **Case 2**

### *History*

A 6-year-old 574 kg Belgian Warmblood mare was presented at the Department of Large Animal Internal Medicine, Ghent University, with a history of weight loss and partial anorexia for the last 4 weeks. In the last week, the horse had also had episodes of fever (up to  $39.6^\circ\text{C}$ ), which was not responding to ceftiofur (Excede®) and flunixin meglumine (Meflosyl 5%®). On clinical examination the horse had a body score of 3/9 (Henneke Body Scoring Condition), a body temperature of  $38.0^\circ\text{C}$ , a heart rate of 48/min and a respiratory rate of 20/min. The mucous membranes were normal. The packed cell volume was 27% (ref. values: 32-53%), with a red blood cell count of  $6.0 \times 10^{12}/\text{liter}$  (ref. values:  $6-12.9 \times 10^6/l$ ) and hemoglobin concentration of 99 g/l (ref. values: 110-190 g/l). The total white blood cell count and differentiation were normal. The biochemical blood analysis remained within normal limits, except for a mild increase of the gamma fraction of the total protein (2.1 g/dl) (ref. values: 0.55-1.9 g/dl). The thoracic sounds were slightly increased and



**Figure 1. Case 2. Rectal ultrasonography of two different masses taken with a 7.5 MHz and a display depth of 8 cm. Arrows: abnormal masses along the echolucent aorta**

the abdominal sounds were normal. Rectal examination revealed 4 well delineated masses (5-15 cm in diameter) along the abdominal aorta and in the vicinity of the left kidney. The ureter could not be located, and the urinary bladder felt normal. The urine was yellow with a specific gravity of 1.022 and a pH of 8. The results of urine analysis with a reagent strip revealed a protein reaction of 1+. Hemoglobin, glucose, ketone bodies, bilirubin and urobilinogene were negative. The cytologic examination was unremarkable. Fractional urinary excretion of sodium, potassium and calcium were within normal reference ranges. Transthoracic ultrasonography showed comet tails in both lungs, being more pronounced in the right lung. On thoracic radiography, numerous localized opacities with a micronodular aspect were observed within the dorsal parts of the caudal lung lobes. Upper respiratory tract endoscopy was unremarkable. Broncho-alveolar lavage fluid analysis revealed a white blood cell count of  $528/\text{mm}^3$  with 46% neutrophils, 8% lymphocytes, 42% macrophages and 4% epithelial cells. Bacteria or atypical cells were not present. Transabdominal ultrasonography showed some free fluid, as well as an indistinct mass dorsal to the left kidney. Using rectal ultrasonography, several masses were visualized along the abdominal aorta (Figure 1). Echography of the liver showed no abnormalities. On gastroscopic examination, ulceration (grade 2/4) was present along the margo plicatus. Abdominocentesis gave a clear, yellow peritoneal fluid with total protein of 36 g/liter and a white blood cell count of  $0.8 \times 10^9/\text{liter}$ . Cytology of the fluid showed a moderately cell-rich smear on a background of red blood cells. The nucleated cell population con-

sisted of clusters of large polygonal cells with occasional tubule formation. These cells had a large round centrally located nucleus with 3 to 4 nucleoli and vesicular chromatin, the cytoplasm was eosinophilic and occasionally vacuolated. Mitotic figures and multinucleated cells were seen. There was marked anisocytosis, anisokaryosis and anisonucleolosis. A transrectal biopsy on one of the well-delineated masses along the abdominal aorta showed multiple large polygonal cell tubule formations, randomly arranged in a hemorrhagic loose fibrous tissue with no connection to the rectal wall. The histological characteristics of the neoplastic cells were similar to those described for the abdominal fluid. Many tumor cells were apoptotic and there was a mixed diffuse inflammation. A histopathological and cytological diagnosis of adenocarcinoma was made. In a period of six days, the horse lost 39 kg of weight. Because of the poor prognosis, the horse was euthanized.

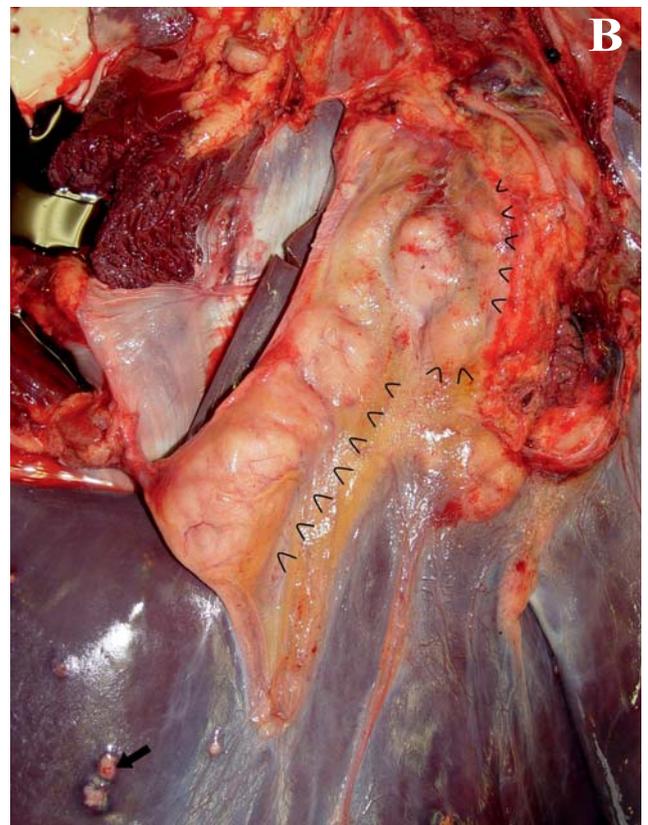
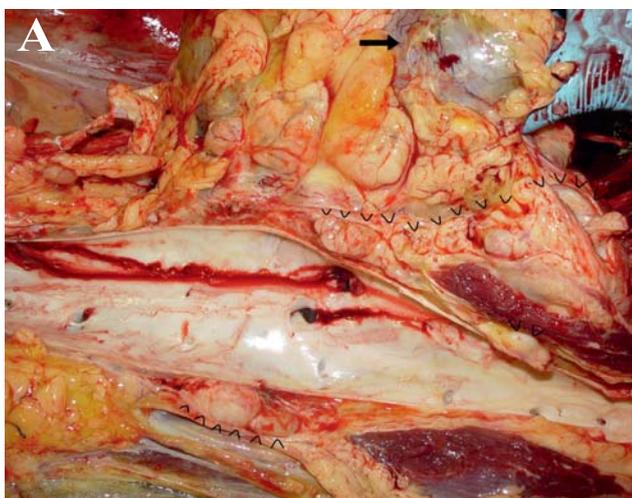
### *Necropsy*

Approximately twenty pale tan masses with a diameter of 5 to 15 cm were encircling the abdominal aorta (Figure 2a), from the diaphragm to the aortic bifurcation. The largest mass was present retroperitoneally ventral to the left kidney, surrounding the proximal part of the left ureter. There was no connection between the renal parenchyma and the masses. The left ureter was uniformly dilated with accumulation of mucus (hydro-ureter), without any grossly visible alterations of the mucosa. The left renal pelvis was mildly dilated. The urinary bladder and renal parenchyma were normal. Multiple 1 to 2 cm diameter nodules were randomly distributed throughout the liver. Larger (4 to 5 cm diameter) masses were present along the course of the adventitial surface of the vena portae (Figure 2b). Pulmonary metastases measuring 2 to 4 mm in diameter were uniformly spread throughout all the lung lobes. Additionally, there was an ulcerative gastritis.

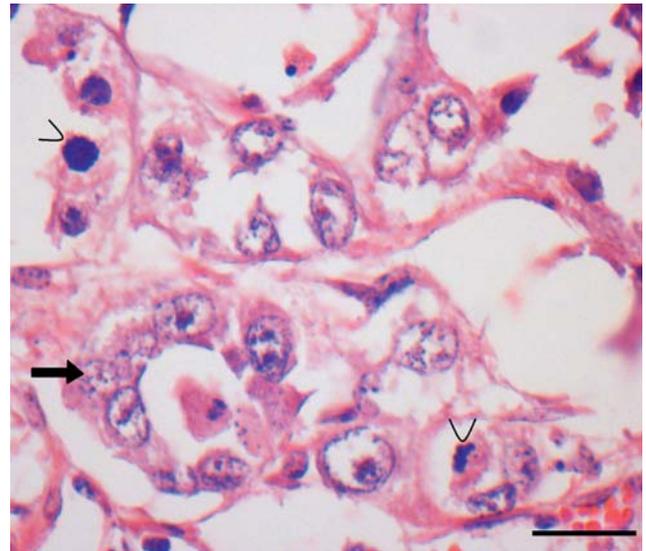
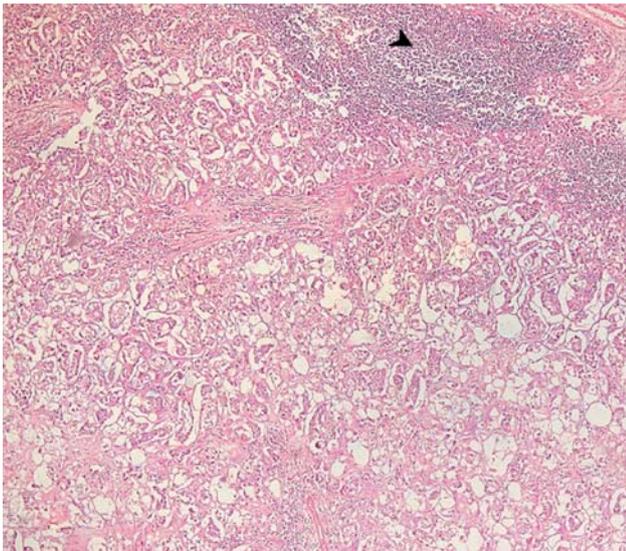
### HISTOPATHOLOGY AND PCR

Formalin fixed and paraffin wax embedded tissue samples from the retroperitoneal masses encircling the ureter in cases 1 and 2, the intra-abdominal and pulmonary metastases in cases 1 and 2, and the liver metastases in case 2 were histopathologically examined.

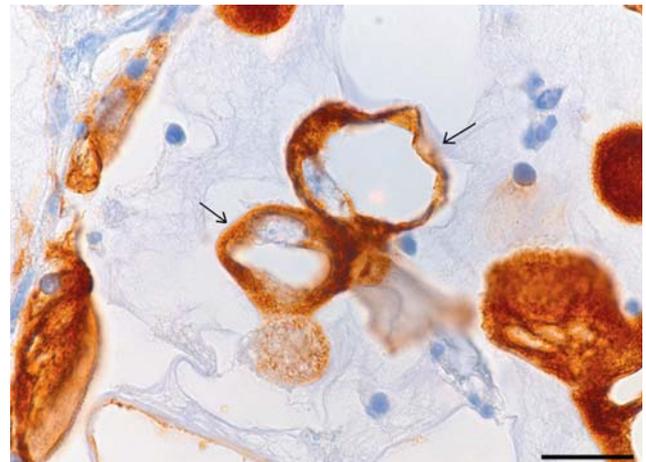
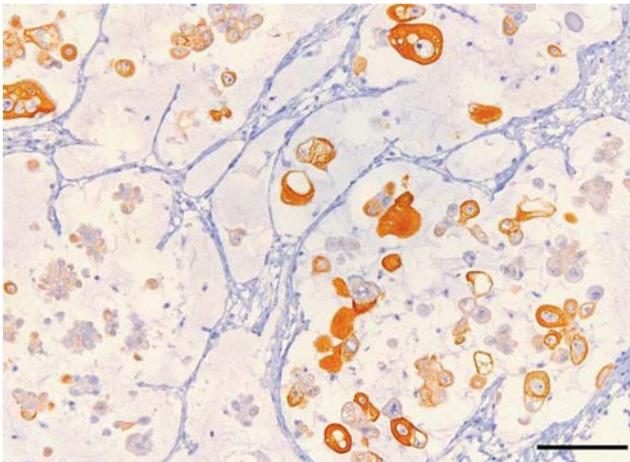
The retroperitoneal masses surrounding the ureter from both cases were defined as multinodular, poorly demarcated, non-encapsulated, densely cellular and infiltrative. They consisted of large polygonal epithelial cells predominantly forming nests in a moderate amount of loosely arranged fibrovascular stroma (Figure 3a). The tumor cells had a large round central to slightly eccentric vesicular nucleus, with 1 to 5 prominent nucleoli and vesicular chromatin. The cells had an abundant amount of eosinophilic cytoplasm with sharp cell borders. Several neoplastic cells contained large cytoplasmic vacuoles giving a 'signet cell' appearance (Figure 4b). There was marked nuclear and cell atypia with frequent syncytial cell formation. The mitotic index ranged from 2 to 4 per high power field, with the presence of bizarre mitotic figures. In both cases, tubulus formation often occurred (glandular metaplasia) (Figure 3b). Small lumina, sometimes filled with PAS-positive mucinous material, were lined by 1 to 3 tumoral epithelial layers. In both cases, there were large areas of necrosis and hemorrhage, diffusely infiltrated by neutrophils. Many individual tumor cells were apoptotic. At the periphery of the lesions, there was lymphoplasmacytic inflammatory infiltrate. Histo-



**Figure 2.** Case 2. (A) Pale tan masses in the perirenal area, extending along the aorta and v. cava caudalis (small arrows). Kidney on top of the picture (arrow). (B) Masses along the v. portae (small arrows) into the liver parenchyma (arrows)



**Figure 3. Case 2. (a) Overview of peri-ureteral mass. Large polygonal cells growing in nests in abundant fibrovascular stroma. Lymphoplasmacytic inflammation at the periphery (small arrow). H & E stain. Bar = 500µm. (b) Detail of mass with multifocal tubule formation (glandular metaplasia, see arrow). Two mitotic figures are present (small arrows). H & E stain. Bar = 50µm.**



**Figure 4. Case 1. (a) Peri-ureteral mass. Diffuse intracytoplasmic cytokeratine HMW immunoreactivity with variable intensity. IHC. Bar = 100µm. (b) Detail of neoplastic cells with signet cell appearance (arrows). IHC HMW cytokeratin. Bar = 20µm.**

pathology of the ureters in case 2 revealed no abnormalities, although no serial sectioning was performed. Intra-abdominal, pulmonary and hepatic metastases were non-encapsulated and highly invasive in the parenchyma. The histological characteristics of the metastatic tumor cells were similar to these of the primary retroperitoneal tumor. A histological diagnosis of TCC was made. Immunolabeling for pancytokeratin (AE1/AE3) and High Molecular Weight cytokeratin (HMW, Clone 34BE12) expression was evaluated (DakoCytomation, monoclonal mouse anti-human, Glostrup, Denmark). Diffuse cytoplasmic cytokeratin and cytokeratin-HMW expression was established in the tumor cells in both cases (Figure 4a). Additionally, immunohistochemistry for the demonstration of Uroplakin-3 (UP-3) using a commercially available kit (Acris Antibodies GmbH, Herford, Germany) was performed. Samples from both cases, as well as positive control horse transitional epithelium were negative for UP-3.

PCR analysis for bovine papilloma virus (BPV)-DNA and equine papilloma virus 2 (EcPV2)-DNA was performed at the Department of Surgery and Anesthesia of Domestic Animals, Faculty of Veterinary Medicine, Ghent University. DNA was extracted from the paraffin embedded material by means of a commercial protocol (Puregene® DNA Isolation Kit, Gentra Systems) resulting in a DNA pellet which was dissolved in a final volume of 100µl. A PCR with a primer-set amplifying a common sequence of the E5L2 open reading frame of both BPV-1 and BPV-2 was performed according to Bogaert *et al.* (2005). EcPV2-DNA was detected using a primer set amplifying a 679 base pair fragment of the E1 gene, as described by Vanderstraeten *et al.* (2010). In neither of the two samples could BPV-DNA or EcPV2-DNA be detected.

## DISCUSSION

This report describes two unusual cases of equine

TCC with intra-abdominal dissemination and pulmonary metastases in both cases, and liver metastasis in one case. In both horses, the largest masses were located ventral to the kidney without any connection between the tumor and the renal parenchyma. The primary masses surrounded the ureter in both cases, though no direct proof of ureteral origin was found on histopathology. Since (1) no other masses were present in the urinary tract (nor at any other places lined by transitional epithelium, such as the nasal cavity), (2) the largest masses were present in the vicinity of the ureters, and (3) the histopathology was typical for TCC, primary ureteral origin was considered most probable. In human medicine, TCC is divided according to the TNM classification system into non-invasive TCC restricted to the mucosa (Ta and Tis), and invasive TCC (T1-T4) (AJCC, 2006), of which T3 and T4 invade through the ureteral wall, and often do not bulge into the lumen (See and Williams, 1992). In these cases, the neoplastic mass is adjacent to an intact ureter. Assuming ureteral origin, the two cases described in this paper might be classified as invasive TCC T3. Additionally, N3 and M1 grades can be given to regional lymph node metastases and distant metastases, respectively.

Early metastasis of TCC occurs via lymphatic vessels (AJCC, 2006), which explains the multiple masses encircling the abdominal aorta in these two cases. A similar metastatic pattern has been described previously in horses with urinary bladder TCC (Traub *et al.*, 1983; Turner *et al.*, 1995; Patterson-Kane *et al.*, 2000). Hematogenous spread can occur later in the course of the disease (Traub-Dargatz, 1998), explaining lung and liver metastases in the present cases.

Identification of neoplastic urothelium is based on anatomic locations, cellular morphology and immunohistochemistry. Immunohistochemical markers such as pancytokeratin and HMW cytokeratin are indicative but not specific for urothelium. In the present case, neoplastic cells were positive for both markers. In human medicine, and in dogs and cows, the identification of urothelium is performed by the demonstration of uroplakins (Ambrosio *et al.*, 2001; Ramos-Vara *et al.*, 2003). Unfortunately, UP-3 was not able to stain equine urothelium.

In humans and dogs, environmental and genetic risk factors for ureteral TCC have been identified, such as topical insecticides, obesity, female gender and breed in dogs (Colin *et al.*, 2009; Mutsaers *et al.*, 2003). Ureteral TCC induction in dogs has been described following the administration of chemical carcinogens such as Cesium Chloride (CsCl) (Hanika and Rebar, 1980; Scott and Boyd, 1953). Urinary bladder tumors in cattle and sheep are associated with enzootic hematuria due to the ingestion of bracken fern (*Pteridium aquilinum*) (Traub-Dargatz, 1998). The relationship between bracken fern ingestion and the occurrence of TCC in horses is less clear (Patterson-Kane *et al.*, 2000). In these cases, no history of possible bracken fern ingestion is known. In cattle, urinary bladder tumors also have been linked with Bovine Papillomavirus (BPV) infection (Borzac-

chiello and Roperto, 2008). In horses, the occurrence of equine sarcoid has been linked with BPV infection (Chambers *et al.*, 2003). Recently, the presence of Equine Papillomavirus type 2 (EcPV2) DNA was demonstrated in equine squamous cell carcinomas (Vanderstraeten *et al.*, in press). In our cases, PCR analyses for BPV-DNA and EcPV2-DNA were both negative. Both horses were female, indicating a possible predisposition to gender. However, more cases should be included.

In conclusion, ureteral TCC in horses has malignant behavior, with local and distant metastasis. Pancytokeratin and HMW cytokeratin are reliable markers, even in poorly differentiated cases such as these, and UP-3 might not be useful as a marker of equine urothelium.

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## Persbericht

### MERIAL Parasitology Award 2011 uitgereikt aan Johannes Charlier

**Dr. Johannes Charlier, wetenschappelijk onderzoeker bij het Laboratorium voor Parasitologie van de Faculteit Diergeneeskunde, Universiteit Gent heeft de MERIAL-Award 2011 voor parasitologie ontvangen. Aan de prijs zijn een oorkonde en een bedrag van 3000 euro verbonden.**

De MERIAL Award voor parasitologie wordt jaarlijks toegekend aan een gepromoveerde onderzoeker uit de Benelux die belangwekkend en innovatief werk heeft verricht. Dit jaar is de MERIAL-Award, die voor de veertiende maal werd uitgereikt, naar Johannes Charlier gegaan.

Deze "Merial Parasitology Award 2011" werd op donderdag 26 mei uitgereikt in Dalfsen (NL) tijdens het lustumsymposium van de Nederlandse Vereniging voor Parasitologie (NVP) dat ter ere van haar 50-jarige bestaan werd georganiseerd. De award werd toegewezen aan Dr. Johannes Charlier voor zijn onderzoek naar worminfecties bij rundvee.

In de afgelopen tien jaar heeft het onderzoek van Johannes Charlier geleid tot nieuwe diagnostische technieken en inzichten die vandaag reeds in de praktijk worden toegepast. In de toekomst wil hij zich verder toeleveren op de gevolgen van parasitaire infecties op de algemene economische efficiëntie van onze veeteeltbedrijven. Het aangepast omgaan met endemische parasitaire ziekten zal een belangrijke rol blijven spelen in de optimalisering van de productieprocessen op veeteeltbedrijven.