

ULTRASONOGRAPHIC FINDINGS RELATED TO PROGNOSIS IN CANINE TRANSITIONAL CELL CARCINOMA

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In human bladder cancer patients, ultrasonography is extensively used not only to identify tumor masses but also to evaluate tumor size, shape, echogenicity, location, and degree of tumor invasion into the bladder wall. The information revealed by ultrasonography delineates the tumor's biological features and facilitates prediction of prognosis. However, in veterinary medicine the feasibility of using ultrasonography for these purposes has not been fully investigated. In this retrospective study, we reviewed cases of dogs with histologically confirmed bladder mass lesions, including transitional cell carcinoma ($n = 22$) and polypoid cystitis ($n = 5$), to determine whether ultrasonography could reliably predict bladder wall involvement. By following patients with transitional cell carcinoma until death, we also determined whether ultrasonographic tumor size, shape, echogenicity, and mass location were related to prognosis. Wall involvement as revealed by ultrasound was significantly ($P = 0.00005$) associated with histological muscular layer involvement with a sensitivity of 93% (95% Confidence interval, 79–98%) and specificity of 92% (95% Confidence interval, 76–98%). Ultrasonographic wall involvement ($P = 0.03$, vs. noninvolvement), heterogeneous mass ($P = 0.02$, vs. homogeneous mass), and trigone location ($P = 0.01$, vs. other locations) characteristics were significantly associated with shorter survival times in transitional cell carcinoma cases. Findings indicated that ultrasonographic characteristics such as wall involvement, heterogeneous mass, and trigone location could be reliable prognostic indicators in canine transitional cell carcinoma. © 2013 American College of Veterinary Radiology.

Key words: canine, prognosis, transitional cell carcinoma, ultrasonography.

Introduction

TRANSITIONAL CELL CARCINOMA is the most common form of canine urinary bladder tumor, accounting for 50% to 75% of all reported bladder tumors.^{1,2} Squamous cell carcinoma, adenocarcinoma, undifferentiated carcinoma, leiomyoma, leiomyosarcoma, and rhabdomyosarcoma are observed less frequently.^{3–5} Canine transitional cell carcinoma is generally aggressive with invasive and metastatic features,² while in humans approximately 80% of bladder tumors are superficial without deeper invasion into the bladder wall.⁶ Aggressive transitional cell carcinoma, which has the potential of metastasizing to regional lymph nodes, lung, and other organs, is not common in human medicine.⁷ Superficial tumors generally respond well to local endoscopic resection with or without adjuvant chemotherapeutic agents, whereas aggressive infiltrating tumors are managed with curative cystectomy in early stages or with palliative therapy by chemotherapeutic agents and

radiation in advanced stages.⁸ Because treatment options and prognosis are very different for superficial and invasive human tumors, it is important to know at the time of diagnosis whether patients have invasive or superficial tumors in order to choose the appropriate course of treatment or to predict the clinical outcome.

Transabdominal ultrasonography, which is an excellent procedure for identifying and evaluating tissue structural abnormalities of abdominal organs, has been used extensively for preoperative tumor-node-metastasis (TNM) staging of human bladder tumor patients.⁹ This imaging technique can provide clinical information on bladder wall invasion (T stage) and lymph node enlargement (N stage).^{10–15} Provisional TNM staging with the imaging technique, along with detection of distant metastatic lesions in the liver (M stage), is clinically valuable because advanced TNM stage in human bladder tumor patients is closely associated with short-survival times.^{16–19} Recently, in addition to these imaging findings used for TNM staging, ultrasonographic characteristics such as tumor size, shape, and echogenicity have also been described as factors for predicting prognosis.^{20–23}

Based on the fact that most cases of canine transitional cell carcinoma are invasive and metastatic, precise

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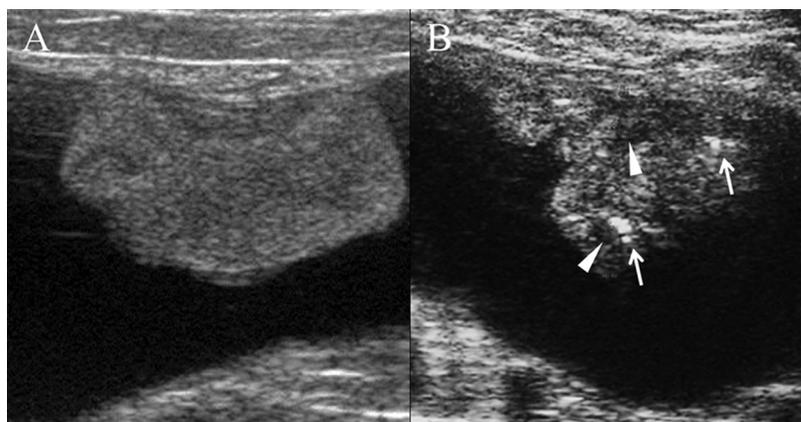


FIG. 1. Ultrasound images demonstrating bladder masses with homogeneous (A) or heterogeneous (B) echo patterns. The homogeneous mass shows uniform echogenicity. The heterogeneous mass shows mixed echogenicity with hyperchoic (arrows) or hypochoic (arrowheads) interior areas.

ultrasonographic evaluation is more important in veterinary medicine for the appropriate assessment of prognosis and treatment, as compared to human bladder tumors.² In particular, because bladder invasion could be a sentinel finding for distinguishing transitional cell carcinoma from other benign lesions such as polypoid cystitis and benign tumors, detailed evaluation of bladder wall invasion is essential for canine bladder masses.

The purpose of this study was to determine whether ultrasonography reliably predicts bladder wall involvement in canine clinical cases with histopathologically confirmed transitional cell carcinoma vs. nonneoplastic disease (polypoid cystitis). Ultrasonographic tumor size, shape, echogenicity, and involved location were also compared to patient survival times. We hypothesized that these ultrasonographic characteristics would be useful for predicting prognosis for dogs with transitional cell carcinoma.

Materials and Methods

Dogs histopathologically diagnosed with transitional cell carcinoma or polypoid cystitis were identified in a search of medical records at the Rakuno Gakuen University Veterinary Teaching Hospital from 2004 to 2011. Detailed histopathological examination was performed for all cases after surgical biopsy. In the transitional cell carcinoma cases, tumor invasion within the muscular layer, necrosis areas within tumor tissues and mitotic count of tumor cells were recorded. Mitotic count was determined by counting the mitotic figures in 50 consecutive high-power fields (hpf) on sectioned tissues stained with hematoxylin and eosin. A count of $\geq 10/50$ hpf was considered “high mitotic count,” referring to a previous report.²⁴ Inflammatory involvement of the muscular layer also was examined in cystitis cases.

Transabdominal ultrasonography was performed preoperatively for all dogs using convex (7.5 MHz) or linear

TABLE 1. Comparison between Ultrasonographic and Histopathological Results in Dogs with Transitional Cell Carcinoma and Polypoid Cystitis

Ultrasonography	Histopathology	
	Involvement <i>n</i> = 14(14/0)*	Noninvolvement <i>n</i> = 13(8/5)*
Involvement <i>n</i> = 14(14/0)*	13 [†] (13/0)	1 (1/0)
Noninvolvement <i>n</i> = 13(8/5)*	1 (1/0)	12 [†] (7/5)

Statistical differences were calculated with the chi-squared test.

*Transitional cell carcinoma/polypoid cystitis.

[†] *P* < 0.0001.

probes (10–13 MHz) connected to a scanner (EUB-6500, HITACHI Medical Corporation, Tokyo, Japan). Dogs were positioned in dorsal recumbency for ultrasonography and examined with distention of the urinary bladder produced by filling it with sterile saline solution (2 ml/kg), in accordance with a previous report.²⁵ Ultrasonographic information including bladder mass size, echo pattern (homogeneous or heterogeneous), tumor shape (pedunculated or nonpedunculated), involvement (involving the bladder wall muscular layer or not), location (trigone or other sites) were obtained from a series of still images, stored movies, and detailed diagnostic comments written by ultrasonographers. Involvement of the bladder wall by ultrasound was diagnosed when ultrasonographic abnormalities were noticed in a hypoechoic layer (muscular layer) of the bladder wall around masses, as described in previous reports.^{10,26} Bladder masses having uniform echogenicity or mixed echogenicity with hyperchoic and hypochoic interior areas were recorded as “homogeneous” or “heterogeneous,” respectively (Fig. 1). For all transitional cell carcinoma cases, overall survival time was calculated from the time of operation until the time of death.

All statistical tests were selected and performed by one corresponding author (T.U.) using commercial software (Statmate III, ATMS Co., Ltd., Tokyo, Japan). Statistical significance for differences was calculated with the chi-squared test. Sensitivity and specificity were calculated with

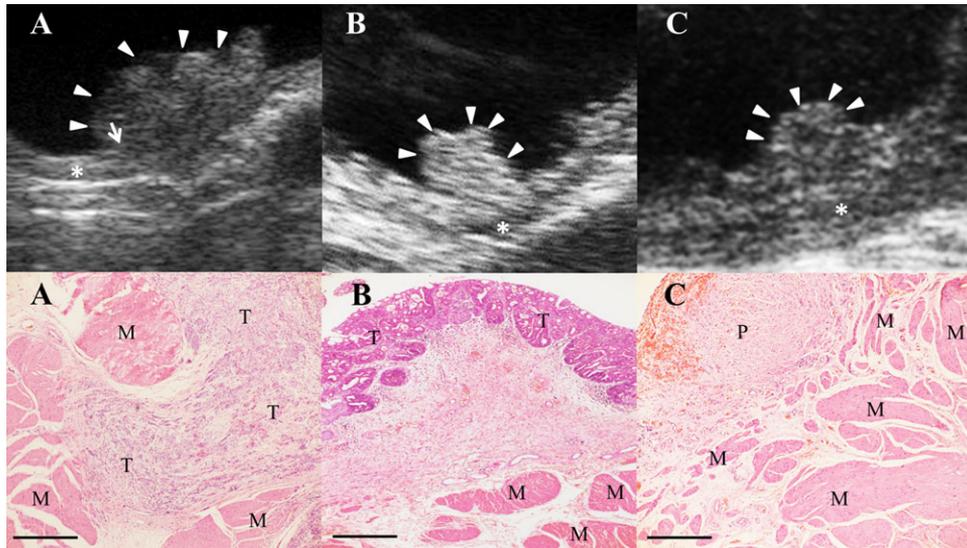


FIG. 2. Representative images obtained by ultrasonography (upper panels) and histopathology (lower panels) in a muscular layer involvement case of transitional cell carcinoma (A) and nonmuscular involvement cases of transitional cell carcinoma (B) and polypoid cystitis (C).

(A) A nonpedunculated mass (arrowhead) apparently extended into the muscular layer (asterisk), evidenced by discontinuity of lamina propria (arrow), was observed (upper panel). Invasion of tumor cells within the muscular layer was confirmed by histopathology (lower panel).

(B) A pedunculated mass (arrowhead) was noticed independently from the muscular layer (asterisk) with hypoechogenicity (upper panel). No involvement by tumor cells within the muscular layer was noticed by histopathology (lower panel).

(C) A nonpedunculated mass (arrowhead) was noticed apart from the muscular layer (asterisk) with hypoechogenicity (upper panel). Inflammatory lesions were noticed independently from the muscular layer.

M: smooth muscle, T: tumor cells, P: polypoid cystitis lesion, Bar = 200 μ m.

a 95% confidence interval (CI). Significance was considered as $P < 0.05$. Survival curves were drawn by the Kaplan–Meier method and the difference among survival curves was analyzed by the log-rank test.

Results

Dogs

A total of 22 dogs with transitional cell carcinoma and five dogs with polypoid cystitis were enrolled in this study because detailed information on their pathology, clinical findings, and preoperative ultrasonography were available. The mean age of the 27 enrolled dogs was 9.1 years (range, 8–13 years). The dog breeds included Shetland sheepdog (three dogs), Maltese (two dogs), Siberian husky (two dogs), Shi-Tzu (two dogs), mixed breed (two dogs), and 16 other breeds (16 dogs). Chief clinical symptoms, which likely resulted from these diseases, were pollakiuria, hematuria, and dysuria. These symptoms were observed in all cases enrolled. The mean follow-up period for transitional cell carcinoma cases was 17.0 months (range, 1–60 months).

Ultrasonographic Evaluation of Muscular Layer Involvement in Transitional Cell Carcinoma and Polypoid Cystitis

Associations between ultrasonographic bladder wall involvement and histopathological muscular layer involve-

ment are summarized in Table 1. Representative images from ultrasonography and histopathology are provided in Fig. 2.

Wall involvement was identified by ultrasound in 14 dogs (all of which were transitional cell carcinoma cases) and was not observed in 13 dogs (eight transitional cell carcinoma cases and five cystitis cases). In 13 (93%) of the 14 cases with ultrasonographic wall involvement, muscular layer involvement by tumor cells was histopathologically confirmed. A discrepancy between histopathological and ultrasonographic findings was found only in one (7%) of the 14 patients with ultrasonographic wall involvement and in one (8%) of the 13 patients with ultrasonographic wall noninvolvement. Ultrasonographic wall involvement was significantly associated with histological muscular layer involvement ($P = 0.00005$) with a sensitivity of 93% (95% CI, 79–98%), specificity of 92% (95% CI, 76–98%), and a correct diagnosis rate of 93% (95% CI, 77–98%). All of the 14 cases (100%) in which the presence of wall involvement was identified by ultrasound were diagnosed as transitional cell carcinoma by histopathology, while eight of the 13 cases (62%) that displayed an absence of wall involvement were diagnosed with transitional cell carcinoma. The remaining five patients (38%) without wall involvement were diagnosed with polypoid cystitis based on pathology.

TABLE 2. Relationship between Ultrasonographic Findings and Survival Times in Dogs with Transitional Cell Carcinoma

Ultrasonography	Survival times (months)
Bladder wall invasion	
Invasion ($n = 14$)	14.6*
Noninvasion ($n = 8$)	38.3
Tumor size	
<20 mm ($n = 12$)	20.5
≥ 20 mm ($n = 10$)	18.9
Echo pattern	
Homogeneous ($n = 13$)	23.2*
Heterogeneous ($n = 9$)	10.7
Shape	
Pedunculated ($n = 13$)	19.3
Nonpedunculated ($n = 9$)	20.2
Location	
Trigone ($n = 11$)	15.2*
Other sites ($n = 11$)	23.9

Statistical differences were calculated with the log-rank test.

* $P < 0.05$.

Relationship between Ultrasonographic Findings and Survival Time in Transitional Cell Carcinoma

Relationships among ultrasonographic findings (bladder wall involvement, tumor mass, echo patterns of tumor mass, mass shape, and involved locations within the urinary bladder) and survival times in the 22 transitional cell carcinoma cases are summarized in Table 2.

Cases demonstrating ultrasonographic bladder wall involvement showed significantly ($P = 0.03$) shorter survival times as compared to those with no wall involvement, with mean survival times of 14.6 and 38.3 months, respectively. Heterogeneous masses resulted in significantly shorter ($P = 0.02$) survival times than homogeneous masses, with mean survival times of 10.7 and 23.2 months, respectively. In 11 of the 22 transitional cell carcinoma cases (50%), involvement of the trigone, which was the most common tumor site, was found. Complications of urinary obstruction were noticed in six of the eleven trigone cases (55%). Cases with trigone involvement had significantly ($P = 0.01$) shorter survival times as compared to dogs with wall involvement in other locations. The mean survival times were 15.2 months for trigone locations and 23.9 months for other locations.

Relationship between Ultrasonographic and Histopathological Findings in Transitional Cell Carcinoma

The relationship between ultrasonographic features and histopathological findings of necrosis and mitotic index (previously reported to be prognostic factors in human bladder cancers²⁷) are summarized in Table 3.

Notable necrosis was confirmed by histopathology in 57% of wall involvement cases (vs. 0% of nonwall involvement cases), 58% of ≥ 20 mm tumor size cases (vs. 8% of <20 mm cases), 67% of heterogeneous cases (vs. 15% of homogeneous cases), and 63% of trigone cases

TABLE 3. Relationship between Ultrasonography and Histopathology Characteristics in Dogs with Transitional Cell Carcinoma^a

Ultrasonography	Histopathology	
	Necrosis ($n = 8$)	High mitotic count ($n = 10$)
Bladder wall involvement		
Involvement ($n = 14$)	8*	8
Noninvolvement ($n = 8$)	0	2
Tumor size		
<20 mm ($n = 12$)	1*	3
≥ 20 mm ($n = 10$)	7	7
Echo pattern		
Homogeneous ($n = 13$)	2*	4
Heterogeneous ($n = 9$)	6	6
Shape		
Pedunculated ($n = 13$)	4*	3*
Nonpedunculated ($n = 9$)	4	7
Location		
Trigone ($n = 11$)	7*	8*
Other sites ($n = 11$)	1	2

^aIn 19 of 22 transitional cell carcinoma cases, bladder lesions were found as a single mass.

*Significantly different at $P < 0.05$.

(vs. 9% of other locations). Individual ultrasonographic findings, including wall involvement ($P = 0.03$), ≥ 20 mm tumor size ($P = 0.03$), heterogenic tumor mass ($P = 0.04$) and involvement of trigone ($P = 0.03$), were significantly associated with transitional cell carcinoma containing histological internal necrosis areas. Furthermore, transitional cell carcinoma with necrosis showed significantly ($P = 0.00004$) shorter survival times when compared to those having no necrosis, with mean survival times of 9.5 and 26.2 months, respectively.

High mitotic index was observed in 72% of the trigone cases (vs. 9% of other cases) and 77% of nonpedunculated cases (vs. 23% of pedunculated cases). Trigone involvement ($P = 0.03$) and nonpedunculated tumors ($P = 0.04$) were significantly associated with high mitotic tumors. However, there was no significant correlation between high mitotic count and survival time ($P = 0.2$), contrary to what has been observed in humans.

Discussion

Transabdominal ultrasonography is commonly used as a first-line imaging technique for evaluation of abdominal organs in veterinary medicine because this technique is noninvasive, widely available, and does not require anesthesia. A precise evaluation of tissue structures of the bladder wall is necessary for diagnosing transitional cell carcinoma, so that it can be differentiated from other benign lesions. The canine urinary bladder wall, as observed by contemporary ultrasound, is a three-layered structure. There are two hyperechoic parallel thin layers and a hypoechoic layer that corresponds to the muscular layer between the two

hyperechoic layers.²⁴ Because the muscular layer can be identified by a clear separation from other histological structures through skillfully conducted ultrasound, tumor involvement in the bladder muscular layer can be assessed in most cases. In this study, muscular layer involvement was reliably identified by ultrasound in 25 of 27 cases (93%), and was found to be in accordance with histological results. Disagreement between ultrasonography and pathology was observed in only two cases. One case, in which minor histological involvement was found, was misdiagnosed as “noninvolvement” by ultrasound. In the other case, which had no histological involvement and in which tumor mass was located on the ventral wall of the bladder, was misdiagnosed as “involvement” by ultrasound. Thus it must be understood that ultrasound cannot dependably evaluate microscopic involvement. In addition, because it may be difficult to evaluate the ventral bladder wall near the body surface due to interference by ultrasound reverberation artifacts and decreased near-field resolution with some transducers,¹⁵ there is potential for erroneous results when tumors are located on the ventral wall of the urinary bladder. Notably, in seven of 13 cases (54%) diagnosed as “noninvolvement” by ultrasound, tumor cell invasion into the lamina propria but not the muscular layer were histopathologically confirmed. Considering that bladder lamina propria cannot be distinguished from the mucosal layer, even with high-end contemporary ultrasonography,²⁸ early stage cases of transitional cell carcinoma with microscopic lamina propria invasion cannot be reliably ruled out based only on an ultrasonographic finding of no muscular involvement. Despite these few divergent cases, our results showed that state-of-the-art ultrasonography could identify muscular layer involvement with a high degree of sensitivity. Furthermore, our findings indicated that ultrasonographic bladder wall involvement was significantly associated with transitional cell carcinoma as well as shorter survival times compared to noninvolvement cases. These findings support the use of detailed evaluation of the bladder wall by ultrasound for diagnosis and prediction of prognosis in canine transitional cell carcinoma. The clinical importance of bladder wall evaluation is supported by the observation in human bladder tumors that muscular layer involvement is a clinical factor defining clinical outcomes.^{6, 29, 30}

Prognosis for human urinary bladder tumors is associated with histopathological factors such as the mitotic

index of tumors and the presence of necrotic area.²⁷ Consistent with findings in previous human studies, the presence of necrosis areas in canine transitional cell carcinoma cases was significantly associated with poor prognosis in the current study. Based on our histologic finding that necrosis areas were found within large or heterogeneous transitional cell carcinoma masses, ultrasonographic size and echogenicity of tumors might be markers for predicting the prognosis of transitional cell carcinoma. Indeed, our statistical analysis identified a significant association between ultrasonographic heterogeneity and shorter survival time.

A possible explanation for poorer prognosis in cases of large and heterogeneous transitional cell carcinoma may be that biologically aggressive tumors tend to grow rapidly and contain areas of necrosis.^{27, 32} Also, tumors with many areas of interior necrosis are commonly detected as heterogeneous masses by ultrasound.^{31, 33–36} Many other biological and clinical factors such as local invasion, distant metastasis, and urethral blockage may also have a negative influence on the prognosis. In humans, heterogeneous echogenicity has been described as an ultrasonographic marker indicating potential malignancy.^{37, 38}

Involvement locations including the prostatic urethra, bladder neck, posterior wall, and trigone area are related to poor prognoses in humans.³⁹ Similarly, canine trigone involvement was significantly associated with short-survival time in dogs of the current study. Involvement of the bladder trigone, the most common site for canine transitional cell carcinoma, eventually leads to partial or complete urinary tract obstruction.⁴⁰ In fact, in more than half of the trigone involvement cases, urinary tract obstruction with complications of uremia and pyelonephritis, which often negatively affect prognosis, were noted.⁴¹

In conclusion, although this study was retrospective and targeted at a limited population, our results indicated that evaluation of bladder wall involvement by ultrasound, along with other ultrasonographic findings including heterogeneous mass and trigone location, could be reliable indicators of prognosis in canine transitional cell carcinoma.

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