Submucosal resection via a transanal approach for treatment of epithelial rectal tumors – a multicenter study

SUBMUCOSAL RESECTION VIA A TRANSANAL APPROACH FOR TREATMENT OF EPITHELIAL RECTAL TUMORS - A MULTICENTER STUDY

Abstract

Objective

Several surgical techniques are described to treat canine rectal masses. Recent recommendations suggest that submucosal resection via a transanal approach should be reserved for benign masses, with limited published data on submucosal resection of malignant masses. The aim of this study was to evaluate complications and long-term outcome after submucosal resection of benign and malignant epithelial rectal masses.

Study design

Retrospective multicentric study.

Animals or sample population

Ninety-three (n = 93) dogs.

Methods

The databases of 7 referral hospitals were reviewed. For survival analysis dog tumors were categorized as benign, carcinoma in situ and carcinoma. The Kaplan–Meier survival curve and Cox proportional hazards analysis were used to determine the association of a range of variables with recurrence and survival time.

Results

Twenty-seven dogs (29%) developed complications. Recurrence was identified in 20/93 (21%), with 12/20 recurrent masses undergoing repeat submucosal resection. Median survival was not reached in any group. Carcinomas had a significantly shorter survival than benign tumors (P = .001), but not carcinomas in situ. The 1-,2-, 5-year survival rates for carcinomas were 95%, 89% and 73% respectively. Dogs developing a complication (P =

.032) or having incomplete margins (P = .023) were associated with an increased risk of recurrence. Recurrence was associated with an increased risk of death (P = .046).

Conclusion

Submucosal resection of both benign and malignant rectal masses is associated with a low rate of severe complications and prolonged survival.

Clinical significance

Submucosal resection via transanal approach is a suitable technique for resection of selected rectal masses.

Keywords: RECTAL TUMOR TRANSANAL SUBMUCOSAL RESECTION

INTRODUCTION

Rectal tumors account for less than 10% of all canine tumors.[1-5] More than half of colorectal masses are malignant,[1,2,6] with adenocarcinoma being the most common.[1,2,4] Multiple surgical techniques have been described for removal of rectal masses including transanal rectal eversion and submucosal resection, dorsal inverted U approach, caudal abdominal approach combined with pubic symphysiotomy or bilateral pubic and ischial osteotomy, rectal pull–through procedure, transanal pull–through procedure, and Swenson´s pull-through and modifications.[2,6-15] Most of these surgical techniques are invasive with complication rates as high as 100% in some reports.[11,14,16,17,21] Recent literature has supported more aggressive techniques for removal of malignant rectal masses with the recommendation that rectal eversion with submucosal resection should be limited to benign masses.[16-18] Two out of these three references are, however, recent textbook chapters which, although lacking a significant body of literature to support the recommendations, can nonetheless influence opinion and surgeons' decisions. .A recent article on transanal rectal pull-through reported a median survival time of 696 and 1006 days after removal of rectal carcinomas and carcinomas in situ respectively, but significant complications and peri-operative mortality were reported.[17] Information on the outcome of conservative surgeries such as submucosal resection via a transanal approach for removal of benign and malignant masses is limited to two small case series with only one including a small number of malignant tumors.[6,19]

The treatment algorithm for the management of human rectal masses is much more refined, with different treatment options based on location (high rectal versus low rectal) and stage (early stage versus advanced stage).[20] Preoperative staging with magnetic resonance imaging (MRI) and endoscopic rectal ultrasound are critical to determine whether a multimodal or surgical first approach is indicated.[21, 22] The morbidity and functional impairment associated

with radical surgery for low rectal masses in people has led to an increased interest in less invasive options such as transanal surgery. However, specific indications and more importantly contraindications have been defined to ensure that a less invasive surgery does not compromise the outcome, especially where a more radical surgery could be curative.[23,24] Unfortunately a treatment algorithm based on patient specific or tumor specific factors is not available in dogs to guide the veterinary surgeon's decision making. Conclusions drawn from human research may not be applicable in dogs because the biological behavior of rectal masses in dogs might differ.

The aim of this study was to report the long-term outcome following submucosal resection via a transanal approach in a large population of dogs and to identify factors associated with recurrence and survival.

We hypothesize that submucosal resection via a transanal approach is a suitable surgical technique to treat benign and malignant rectal masses and is associated with a low complication rate and good long-term outcome.

MATERIALS AND METHODS

Study design and eligibility criteria

This retrospective observational study was approved by the RCVS Ethics Review Panel. The medical record databases of 7 referral hospitals from Italy and United Kingdom were reviewed to identify dogs that underwent submucosal resection of epithelial benign or malignant masses via a transanal approach between June 2006 and June 2019. Dogs were excluded if they presented with rectal tumors of non-epithelial origin, if the tumor was removed with any surgical procedure other than submucosal resection via a transanal approach, or if the mass was already a recurrence at the time of presentation.

Medical records review

Data retrieved from the medical record included signalment, body weight, clinical history, duration of clinical signs, examination findings, diagnostic procedures performed, size of the mass, distance from the anocutaneous junction, surgical time, histopathological results for the excised mass, completeness of excision, duration of hospitalization, postoperative complications, recurrence or metastasis, follow-up time, survival time, and cause of death. Postoperative complications were defined as transient if they resolved and permanent if they persisted until death or last follow-up. Complications were classified as minor, if they spontaneously resolved or required medical treatment, and major if they required revision surgery. Histopathology of samples obtained during colonoscopy versus histopathology of the excised mass were compared. The excision was considered complete if no microscopic tumor cells were noted at the margin and incomplete if tumor cells were identified at the margin. All histopathology samples were assessed and reported by Diplomates of the American or European College of Veterinary Pathologists.

Surgical technique

Dogs were placed in sternal recumbency with the tail bandaged and reflected cranially. The rectal wall was everted through the anus via traction with Babcock or Allis tissue forceps or stay sutures. Sequential placement of further stay sutures was needed in some cases to achieve adequate exposure. Once the mass was exteriorized, a marginal elliptical incision of the mucosa and submucosa was performed around the mass with up to 10 mm lateral margins using a combination of sharp and blunt dissection. Apposition of mucosa and submucosa was performed in one layer using a simple interrupted or simple continuous suture pattern with absorbable monofilament material.

Statistical analysis

Outcome of interest for each dog included diagnosis, complications, time to local recurrence, time to metastasis, and survival time. All times were calculated from the date of surgery to the event (local recurrence, metastasis or death) or when lost to follow-up. The cause of death was classified as either related or unrelated to the disease. Disease-related deaths were further classified as associated either with surgical complications or with the disease itself. For dogs with incomplete follow-up information, referring veterinarians were contacted and the clinical records from the referring first opinion practice were obtained. When information could not be obtained from the referring veterinarian or referring practice records, the owner was directly contacted using a standardized telephone questionnaire. Referring veterinarians and/or owners were contacted, if necessary, in the time period between September 2019 and August 2020.

Analyses were performed using Microsoft Excel 2020 and SPSS 26.0 (IBM SPSS statistics, version 26.0; IBM Corp, Armonk, NY, United States).

Normality was assessed by the Shapiro–Wilk test: datasets likely to be from a normal distribution ($P > .001$) are reported as mean (range), whereas datasets likely not to be from a normal distribution ($P < .001$) are reported as median (range).

A χ^2 test was used to determine any significant association between the categorical variables and the histopathological diagnosis, and a Kruskal-Wallis H test for independent variables was used between all the continuous variables and the histopathological diagnosis. When a significant association was found, Fisher's exact test for categorical variables or Mann-Whitney U test for continuous variables were used to characterize the results.

For survival analysis dogs were grouped in 3 categories based on the histopathology of the rectal mass: benign rectal epithelial mass (which included dogs with rectal hyperplasia and rectal adenoma), carcinoma in situ (CiS) and rectal carcinoma. Rectal masses were classified as CiS if they contained marked cell dysplasia but they remained confined by the basement membrane and did not show an invasive phenotype.[5]

For each dog, disease free survival (DFS) was determined to be the time from the date of surgery to the date of recurrence or censorship; overall survival (OS) was determined to be the time from the date of surgery to the date of death or censorship. Dogs were censored from analysis if they were alive at the time of analysis, died for reasons unrelated to the rectal mass or were lost to follow-up. The Kaplan–Meier method and Cox proportional hazards analysis were used to determine the association of a range of variables with the recurrence and the survival time. The outcome variable was either DFS or OS, and the explanatory variables were size of the mass, distance from the anus, surgical time, diagnosis (benign epithelial rectal mass vs CiS vs rectal carcinoma), margins (complete vs incomplete), complications and recurrences. All variables were initially tested separately via univariate Cox proportional hazards analysis, and a multivariate Cox proportional hazards model was then built, which

145 initially included the variables identified as $P < .2$ on univariate analysis. Cox proportional
146 hazards analysis results are reported as odds ratios, 95% confidence intervals, and the
147 associated P -value. Significance was set at $P < .05$ for two-sided analyses.
148

RESULTS

Animals - Ninety-three dogs fitting the inclusion criteria were enrolled in the study. Each center contributed between 2 and 30 cases. The male to female ratio was 1.44:1 (5 entire females, 33 spayed females, 23 entire males and 32 castrated males). The mean age at the time of initial evaluation for the study was 93.1 ± 33.1 months, and the median body weight was 20 kg (range, 6-64.6). A variety of breeds were represented, including crossbreed (16); West Highland White Terrier (12); Labrador Retriever (9); Cocker Spaniel (6); Golden Retriever (4); English Springer Spaniel, Border Collie, Boxer (3 each); British Bulldog, Bullmastiff, French Bulldog, German Shepherd, Jack Russel Terrier (2 each); and other breeds represented by one individual.

Presurgical clinical findings – The most common clinical signs were hematochezia (n=82 [88.2%]), tenesmus (n=31 [33.3%]), dyschezia (n=12 [12.9%]), persistent rectal prolapse (n=12 [12.9%]), mass prolapse (n=10 [10.7%]), diarrhea (n=10 [10.7%]), anal pruritus (n=3 [3.2%]), rectal protrusion/prolapse after defecation (n=2 [2.1%]), mucoid feces (n=2 [2.1%]), perianal pain (n=1 [1.1%]), weight loss (n=1 [1.1%]), melena (n=1 [1.07%]), stranguria (n=1 [1.1%]) and vomiting (n=1 [1.1%]). Median duration of clinical signs was 8 weeks (range, 0-96).

Rectal abnormalities were detected on rectal digital palpation in 89 (95.7%) dogs, with a palpable mass in 88 (94.6%) and an abnormal/irregular rectal wall in 1 (1.1%) dogs. Digital rectal palpation was unremarkable in one dog while information was not available in 3 dogs. Median maximum tumor diameter was 1.9 cm (range, 1-6). Median distance of the tumor from the anocutaneous junction was 2 cm (range, 1-7). None of the tumors presented with an annular morphology.

Thoracic radiographs were obtained in 20 (21.5%) dogs, abdominal radiographs in 7 (7.5%) and the area assessed and radiographic projections were not specified in 8 (8.6%). No metastatic lesions were identified on radiographs. Abdominal ultrasonography was performed in 48 (51.6%) dogs. Six of these dogs had evidence of lymphadenomegaly affecting the mesenteric lymph nodes (3), colic lymph nodes (2) and medial iliac lymph node (1). Ultrasound-guided fine-needle aspiration of enlarged lymph nodes was performed in 3 dogs, and identified metastatic disease affecting the colic lymph node in 1 dog with rectal carcinoma. Abdominal and thoracic computed tomography (CT) was performed in 8 (8.6%) dogs and metastatic lesions were not identified in any dog. Five of these dogs presented with mild lymphadenopathy on CT affecting the colic (2), cranial mediastinal (2), right axillary (1), sternal (1) and sacral (1) lymph nodes but sampling was not performed. Twelve out of 21 dogs (57.1%) with malignant tumors underwent both thoracic (radiographs or CT) and abdominal imaging (ultrasound or CT). The remaining 9 (42.9%) underwent only thoracic or only abdominal imaging.

Endoscopy was performed in 56 (60.2%) dogs, with identification of the rectal mass in all. Other abnormalities were detected in 4 patients and included edema affecting the distal rectum, small focal erythematous areas on the distal colon, focal areas of erythema and edema in the gastric and duodenal mucosa and a proliferative ulcerated/inflamed region orad to the rectal mass.

Fine-needle aspirates of the rectal masses were performed in 5 (5.4%) dogs and cytological evaluation revealed carcinoma or suspected carcinoma in 4 dogs, and was suggestive of plasmacytoma or inflammatory disease in 1 dog. Preoperative fine-needle aspirates of the rectal mass were consistent with the postoperative histology in 2/5 of the dogs (rectal carcinoma in both cases). Pre-surgical biopsies were performed in 42 (45.2%) dogs, with

196 results being consistent with definitive diagnosis in 27/42 (64.3%). Biopsy results were non-
197 diagnostic in 1/42 (2.4%) dog, and the biopsy report was not available for 1/42 (2.4%) dog.
198 The pre-surgical biopsy results differred from the postoperative biopsy results in 13 cases
199 (31%). The pathologist changed their diagnosis from a benign non-neoplastic diagnosis
200 (hyperplasia, n=1 and lymphoplasmacytic inflammation, n=1) to adenoma in 2/13 (15.4%)
201 cases, from a benign diagnosis (adenoma, n=3) to carcinoma in situ in 3/13 cases (23%),
202 from benign (lymphoplasmacytic inflammation, n=1 and adenoma, n=5) to carcinoma in 6/13
203 cases (46.2%), from carcinoma to adenoma in 1/13 case (7.7%) and from a carcinoma to
204 carcinoma in situ in 1/13 case (7.7%). Overall, the examination of the whole surgical sample
205 was suggestive of a more aggressive pathology in the majority of cases (69%) where a
206 discrepancy between pre-surgical and postoperative samples was present.
207 **Surgical results and complications -** Median surgical time was 25 minutes (range, 10-90).
208 Median postoperative hospitalization time was 1 day (range, 0-6). No intraoperative
209 complications occurred. Twenty-seven out of 93 (29%) dogs developed at least 1
210 postoperative complication. Eighteen dogs developed a single complication, 2 dogs
211 developed 2 complications, and 7 developed 3 complications. Complications were minor in
212 26/27 dogs (96.3%) and major in 1/27 (3.7%). Complications were transient in 26 (96.3% of
213 dogs with complications, 27.9% of dogs in total) and permanent in 1 (3.7% of dogs with
214 complications, 1.1% of dogs overall).
215 Dyschezia was the most common complication affecting 13/93 (14.0%) dogs (transient in
216 12, permanent in 1). Median duration of dyschezia was 24.5 days (range 1-122). Tenesmus
217 was observed in 12/93 (12.9%) dogs, and was transient in all the cases. Median duration of
218 tenesmus was 14 days (range, 2-42). Duration was not reported in 1/12 dog with tenesmus.
219 Other complications included transient hematochezia in 5/93 (5.4%), transient fecal

incontinence 2/93 (2.1%) with a duration of 2 and 10 days, regurgitation in 2/93 (2.1%) dogs, intermittent transient diarrhea in 2/93 (2.1%), rectal prolapse in 1/93 (1.07%), focal superficial perianal dermatitis due to clipping in 1/93 (1.1%) dog, intermittent bleeding and lethargy of 24 hours duration in 1/93 (1.1%) dog each. The only major complication consisted of wound dehiscence in 1/93 (1.1%) dog that prompted revision (primary closure of the dehisced mucosal defect) 5 days after the first surgery.

Histopathologic diagnosis - The 93 masses were classified as follows: rectal hyperplasia (5; 5.4%), rectal adenoma (44; 47.3%), rectal CiS (23; 24.7%), and rectal carcinoma (21; 22.6%). Margin evaluation was available in 86/93 (92.5%). Excision was complete in 63/86 (73.3%) dogs (4 hyperplasia, 31 adenomas, 17 CiS and 11 carcinomas) and incomplete in 23/86 (26.7%) dogs (8 adenomas, 6 CiS and 9 carcinomas).

Follow-up and postoperative outcome - Median follow-up was 708 days (range, 25-4383). Follow-up information until death was available for 43 dogs. For the remaining 50 dogs, 28 had greater than 12 months follow-up time available. Tumor recurrence was identified in 20 (21.5%) dogs: 1/5 (20%) dog with rectal hyperplasia, 6/44 (13.6%) dogs with rectal adenomas, 7/23 (30.4%) dogs with CiS and 6/21 (28.6%) dogs with rectal carcinomas. Margins were incomplete in 8/20 (40%) recurrent tumors, whereas 9/20 (45%) recurred despite histologically complete excision. Margins were not available for 3/20 (15%) recurrent tumors.

Twelve out of 20 (60%) dogs with recurrence had repeat submucosal resection via a transanal approach (1/1 dog with recurrent rectal hyperplasia, 2/6 [33.3%] dogs with rectal adenoma, 5/7 [71.4%] dogs with CiS, 4/6 [66.7%] dogs with rectal carcinoma). Overall reoperation rate for benign masses (hyperplasia and adenomas combined) was 42.9%.

243 Malignant transformation was suspected in two cases: one dog with rectal hyperplasia and
244 one with CiS developed a recurrent mass at the same location 1347 and 761 days after the
245 initial surgery respectively. In both cases, the recurrent mass was re-excised and
246 histopathology was consistent with carcinoma.
247 Of the 21 dogs with rectal carcinomas 1 (4.8%) was diagnosed with preoperative metastatic
248 disease, and 1 (4.8%) developed metastases to lungs, kidney and spleen 761 days after
249 surgery.
250 At the end of the study period 83 dogs (89.2%) were either alive (50 dogs) or the cause of
251 death was unrelated to rectal disease (33 dogs) whereas 10 (10.7%) dogs died for reasons
252 related to the rectal mass. None of the dogs died as a result of surgical complications. Nine
253 out of the 10 cases that died for reasons related to the rectal mass were euthanized due to
254 recurrence (1 adenoma, 3 CiS, 1 CiS that underwent malignant transformation, and 4
255 carcinomas), while 1/10 due to distant metastasis (1 carcinoma). Follow-up information until
256 death was available for 43 dogs. For the remaining 50 dogs still alive at the last follow-up,
257 12 had less than 6 months follow-up information available, 10 had between 6 and 12 months
258 follow-up, 12 had between 12 and 24 months follow-up and 16 had more than 24 months
259 follow-up after surgery.
260 Forty-two of the 50 dogs alive at the end of the study were free of rectal disease at the last
261 follow-up while 7 dogs had evidence of recurrence and 1 dog had clinical signs suggestive
262 of rectal disease. Two dogs with completely excised rectal adenomas, were alive 670 and 693
263 days after surgery despite identification of a recurrence on day 540 and 165, respectively.
264 Three dogs with completely excised rectal CiS were alive 417, 557 and 1580 days after
265 surgery despite identification of a recurrence on day 309, 400 and 286 respectively. One dog
266 with incompletely excised rectal CiS was alive 245 days after surgery but developed

hematochezia at the last follow-up; a recurrent mass was not palpable and repeat endoscopy was declined. Two dogs with completely and incompletely excised rectal carcinomas, were alive 272 and 1135 days after surgery despite identification of recurrence on day 260 and 330, respectively.

Median DFS and OS for dogs undergoing submucosal resection for rectal epithelial neoplasia were not reached. Based on Kaplan–Meier estimates, the 1-, 2-, and 5- year DFS rates were 94%, 89% and 85% for benign tumors, 87%, 70% and 64% for CiS and 75%, 75% and 75% for carcinomas, respectively (Table 1). The 1-,2- and 5-year OS rates were 100%, 97.5% and 97.5% for benign tumors, 100%, 100% and 80% for CiS and 95%, 89% and 73% for rectal carcinomas, respectively (Table 2).

There was no statistically significant difference in the DFS when comparing benign tumors versus carcinomas in situ ($P = .084$), benign tumors versus carcinomas ($P = .78$) or CiS versus carcinomas ($P = .956$) (Figure 1).

There was no statistically significant difference in OS when comparing benign tumors versus CiS ($P = .1$) or CiS versus carcinomas ($P = .956$). However, OS was significantly longer for benign tumors than carcinomas ($P = .001$) (Figure 2).

Risk factors associated with survival of submucosal resection for rectal epithelial neoplasia

Logistic regression analysis was used to determine factors associated with recurrences and survival. After the initial model was refined by backward-stepwise elimination, the best-fit model for recurrences included four variables: surgical time, diagnosis, margins, complications (Table 3). In the final multiple-regression model (Table 4), the only factors associated with an increased risk of recurrence included having a complication ($P = .032$) or incomplete margins ($P = .023$). The best-fit model for overall survival included five

291 variables: surgical time, diagnosis, margins, complications, recurrences (Table 5). In the final
292 multiple-regression model (Table 6), the only factor associated with an increased risk of
293 death included having a recurrence ($P = .046$).
294

DISCUSSION

The results of this study suggest that submucosal resection via a transanal approach is associated with a low rate of severe complications and prolonged survival times for both benign and malignant tumors.

The low complication rate and positive outcome after resection of benign tumors are unsurprising. The use of submucosal resection for treatment of malignant masses is, however, more controversial as this technique does not respect some of the basic surgical oncologic principles regarding treatment of these masses. Achieving an adequate lateral margin may or may not be possible depending on the characteristics of the mass treated and the deep margin is of concern in all cases, given that it will be narrow by definition. Possibly as a result of these concerns, there has been a shift in more recent literature towards more invasive procedures for removal of malignant rectal masses.[5,14,16-18] Morello et al in 2008 suggested that rectal eversion with submucosal resection should be limited to benign masses.[14] Similarly, two recent textbooks suggest that submucosal resection should be reserved for small and superficial benign tumors and possibly selected CiS.[16,18] This recommendation is not fully supported by the available (albeit limited) literature. To our knowledge, there are only two small case series that describe the complications and outcome following submucosal resection via a transanal approach,[6,19] with only one of these including dogs with malignant rectal tumors.[6] In the latter case series,[6] 13 out of 23 cases were carcinomas with recurrence identified in 3 cases 16, 24 and 24 months after surgery respectively. In two of these cases, re-excision was performed. Only one patient died of tumor-related causes 24 months after the initial surgery. The results of our study further support the use of submucosal resection via a transanal approach as a suitable option for the treatment of select rectal carcinomas. In addition to the aforementioned case series as well as our results, Church et al

reported in 1987 on the outcome of treatment of colorectal carcinoma.[25] Twenty-one dogs were treated with 'local excision' which resulted in a mean survival of 22 months, suggesting that a conservative approach is reasonable and can provide good outcome. Unfortunately, the details on the surgical technique, perioperative complications and cause of death in that report were limited. In particular, there is no description of what was considered 'local excision' and whether it included patients undergoing local but full thickness excision and/or partial pull-through surgeries in addition to dogs treated via submucosal resection.

The simplicity, short surgical time and low morbidity of the submucosal resection via a transanal approach make it particularly attractive to both the surgeon and dog owner. Complication rate in the current study was 29%, which is lower than previously reported for transanal submucosal resection. In Danova's study 10/23 (43%) dogs developed minor complications (tenesmus, hematochezia, partial dehiscence) that were managed conservatively.[6] Most dogs in our study developed minor complications and none of the complications resulted in the death of the patient. All minor complications were short lived with only one dog developing permanent dyschezia which required long term medical management. These results compare favorably with more aggressive surgical techniques that have reported complication rates as high as 100% with up to 33% of dogs experiencing permanent complications of which fecal incontinence was the most common.[11,14,17,26] The severity of these complications can result in death or euthanasia.[11,14]

It is unlikely that rectal submucosal resection will be appropriate for all rectal masses. While not specifically investigated in this study, it is intuitive that submucosal resection via a transanal approach is not suitable for annular or deeply infiltrative masses. Indeed, recurrence rate in this study was 21% which is far from negligible. Recurrence rate was higher for rectal carcinomas (28.6%) and for CiS (30.4%); however, repeat submucosal resection was possible

in the majority of cases and only about 10% of dogs died of tumor-related causes. It could be argued that a more aggressive surgery might have reduced the recurrence rate: Nucci et al reported a recurrence rate of 13.7% with partial or complete rectal pull-through, despite more than half of the rectal tumors being malignant.[17] Nonetheless, morbidity was also higher with 7/74 (9.5%) of dogs dying or being euthanized as a result of a complication.[17] Repeat pull-through to address recurrences may further increase morbidity and has not been reported to our knowledge. Conversely, the option to repeat submucosal resection is another advantage of the technique. Repeat submucosal resection was indeed performed in 60% of dogs with recurrence in our study, was well tolerated and prolonged DFS and OS. Another option could be to consider a submucosal resection via transanal approach as the initial approach, and reserve rectal pull-through or alternative approaches for full thickness resection in case of incomplete excision or to address recurrent malignant tumors. This treatment algorithm appears reasonable but has not been explored in our study and it is unknown whether it could result in a better long-term outcome. In people with early stage rectal cancer treated with local transanal excision, salvage radical surgery after a recurrence is identified, is associated with high recurrence rates and poor oncologic outcome.[27] Instead, immediate salvage radical surgery (within 30 days of the local excision) provides oncologic outcomes comparable to matched patients going directly through radical surgery.[28] It is unknown whether the same conclusions would apply to dogs with rectal cancer and further studies are needed.

Based on the available literature, a surgeon presented with a dog with rectal carcinoma faces a decision-making dilemma. We attempted to identify preoperative findings that may predict recurrence and tumor-related death after submucosal resection to provide clinical information that might be used to understand when a more aggressive surgical procedure might be indicated. Unfortunately, none of the preoperative parameters and tumor characteristics was

a predictor for recurrence or survival. Development of complications and incomplete margins on histopathology were the only factors significantly associated with development of a recurrence. Development of recurrence was the only predictor significantly associated with the risk of tumor-related death.

As a consequence, and based on these results, it is currently not possible to preoperatively identify the subset of patients that may benefit from more aggressive procedures. The decision on which surgical technique to adopt remains subjective. Submucosal resection is expected to allow a good outcome in most but not all cases, while ensuring minimal morbidity. A full thickness pull-through is more likely to achieve complete margins which would be expected to reduce recurrence rate and tumor-related death but may increase morbidity-related mortality.

On the contrary, human literature on rectal masses is extensive and has clear indications and, more importantly, contraindications to the use of less invasive local excision techniques. Local excision can be achieved via transanal open or endoscopic procedures such as transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS), as well as via endoscopic submucosal dissection (ESD).[29,30,31,32] Meticulous preoperative staging with MRI and endoscopic rectal ultrasound (ERUS) are critical for staging human patients with rectal cancer, to assess the depth of rectal wall invasion and to channel patients into the most appropriate treatment pathway.[21,22] Advanced imaging is used to classify the tumor according to a clinical T and N classification (cT and cN) which ultimately are the only information available for decision making before surgery. Clinical T based on MRI and ERUS has been proven to correlate well with the pathological T (pT), the T classification based on histopathology of the resected mass, allowing clinicians to identify early stage cancer before surgery.[23]

391 Transanal approaches are considered for early stage low rectal cancer; however even in the
392 subset of patients with T1 or T2 N0 low rectal tumors, radical surgery remains a good option
393 with excellent oncologic and functional outcome when sphincter preservation is possible.[20]
394 Transanal options play a crucial role when location near the sphincter requires perineal
395 resection and permanent colostomy, with the associated high morbidity.[33] The appeal of less
396 invasive procedure should however not compromise the outcome and result in unacceptable
397 high rates of recurrences in situations where a more radical surgery could be curative. For
398 this reason strict case selection is paramount.[23,24] Transanal surgery with local full thickness
399 excision is considered for ERUS staged Tis and T1 lesions that do not have negative
400 prognostic factors (poorly differentiated histology, lymphovascular, or perineural invasion,
401 more than 30% wall involvement, size >3cm).[23] It has to be noted that most human guidelines
402 for treatment of early rectal cancer suggest transanal full thickness (open or endoscopic) local
403 excision, which remains a more aggressive approach and differs substantially from the
404 submucosal dissection procedure in the dogs in the present report. However, an ESD
405 approach to human early rectal cancer is showing promising results and is more comparable
406 from a surgical oncology standpoint to the procedure done in our patients. A recent meta-
407 analysis compared TEM to ESD for early rectal cancer showing that recurrence rates were
408 similar for full thickness versus submucosal excision (5.2 vs. 2.6% respectively; P =.068).
409 However, patients undergoing ESD were less likely to undergo R0 resection (complete
410 histological excision), requiring revision abdominal surgery more often (2.9 vs. 8.4%; P
411 =.011).[32]
412 The biology of rectal masses in dogs might differ from people and further research is needed
413 to develop a staging system that could lead to a treatment algorithm with prognostic
414 significance in dogs. Similar to people, the low morbidity of transanal approaches in dogs is

appealing. In the present study, the metastatic rate was low and tumor related mortality was uncommon. It could be speculated that canine rectal tumor may be biologically less aggressive than their human counterpart. However, the recurrence rates in our dogs would be considered unacceptably high according to human standards and tumor related mortality was not negligible. The veterinary literature should strive to follow the example coming from human publications. It is likely that refining case selection will improve the outcome, reduce the recurrence rate for the patients treated via a transanal approach and identify the high risk patients that would benefit from a more radical surgery.

While not specifically investigated in this study, it is intuitive that submucosal resection via a transanal approach is not suitable for annular or deeply infiltrative masses. In this situation, decision-making for the veterinary surgeon is simpler and options include a pull-through procedure, colorectal resection and anastomosis via pubic symphysiotomy or bilateral pubic and ischial osteotomy or palliative colorectal stenting.[2,6-15,34]

West Highland White Terriers appear to be overrepresented in this study, a finding that concurs with the results of previous studies.[17,26,35] Male to female ratio was 1.44:1. Previous studies have reported that males are overrepresented with ratios of 3:1 to 3.7:1.[1,10,17,19,25,26,35]

The number of dogs undergoing staging procedures was relatively low in this study. Overall only 30% of dogs underwent thoracic imaging (either radiographs or CT). In some cases, staging was not performed because a pre-surgical biopsy was suggestive of benign disease. Furthermore, even in the absence of a pre-surgical biopsy, transanal submucosal resection of rectal masses without extensive investigations is sometimes considered in some of the institutions participating in the study. This is generally decided on a case by case basis and pursued due to a variety of reasons including the relatively high prevalence of benign lesions in the canine rectum, the owner's financial limitations, the owner's reluctance to pursue more

aggressive procedures, regardless of the final diagnosis, as well as an owner's intention to treat for palliation of clinical signs, regardless of whether metastatic disease is present. If after excision a malignant lesion is identified, retrospective staging to discuss potential additional treatment and clarify prognosis is generally recommended. We speculated that this probably explains why the overall numbers of dogs staged is low, however all dogs with rectal carcinoma were staged with 12/21 dogs with carcinoma undergoing both thoracic and abdominal imaging, and the remaining 9 undergoing either abdominal or thoracic imaging. However, it should be underlined that staging in these 9 dogs was incomplete and, as a result, the number of dogs with metastatic disease might have been underestimated.

Sampling of the mass before surgery was often unreliable with only 64.3% of presurgical biopsies consistent with the final histopathologic result. Nonetheless presurgical sampling may remain useful, particularly if addressing large masses that may not be amenable to surgical resection but may respond to medical treatment,[35] such as lymphomas and plasmacytomas.[36,37]

To our knowledge this is the first study that compares the outcome of benign rectal masses versus CiS and carcinomas after submucosal resection. In a previous study on a smaller number of patients, dogs with CiS were more likely to have recurrence of clinical signs after submucosal resection, compared to dogs with rectal adenomas but mass recurrence was not confirmed and statistical analysis was not performed.[19] Dogs with rectal carcinomas were not included in the aforementioned study.

Our study did not identify any significant difference in the DFS between groups (Figure 1). Recurrence was the only predictor for OS but surprisingly, despite the similar recurrence rates across groups, OS was significantly worse for rectal carcinomas compared to benign

tumors (Figure 2). Different hypotheses may explain this finding. It is possible that surgeons and owners may be more inclined to re-operate on a recurrence of a benign adenoma. Conversely re-operation of a carcinoma may be declined due to a perceived need for more aggressive procedures and worse prognosis.

However, the re-operation rate for recurrent carcinomas was higher than for benign tumors, suggesting that an alternative mechanism was responsible for the decreased survival. Analysis of the results revealed that all recurrences in the rectal carcinoma group occurred within a year of surgery. We speculated that early recurrence of malignant masses and a more aggressive biological behavior leading to more rapid growth and progression of the clinical signs, may have led to euthanasia and a shorter survival time than in the other groups.

Rectal CiS were grouped separately due to some controversy on their classification. They are generally classified as benign despite the fact they contain marked cell dysplasia.[5] A previous study suggested that rectal CiS may have a worse biological behavior than rectal adenomas.[19] In our study rectal, CiS appear to display an intermediate behavior between benign and malignant tumors, as apparent on visual assessment of the DFS and OS curves as well as based on assessment of the 1-, 2- and 5- year recurrence and survival rates (Figures 1 and 2, Table 1 and 2).

The major limitations of the present study were inherent with its multicentric retrospective nature. Investigations, staging, operative techniques, peri-operative management and follow-up protocols were not standardized. The measurements of tumor size and distance from the anus were obtained from the clinical notes, surgery reports or referral letters. It is not known how the measurements were obtained and how accurate they were. The histopathological specimens were not reviewed by a single pathologist. However, all samples were assessed and reported by diplomates of the American or European College of Veterinary Pathologists

487 which we believe is sufficient to allow reliable and consistent results for the purpose of the
488 study and better reflects the clinical situation in practice. There might have been a selection
489 bias with smaller masses more likely to undergo submucosal resection rather than more
490 aggressive surgeries. However, larger tumor size was not a predictor for recurrence or
491 survival in our study and the range of tumor size (1-6 cm) and tumor distance from the ano
492 cutaneous junction (1-7 cm) was considered broad and representative of the majority of
493 clinical situations. Furthermore, the demographics and tumor characteristics in our study are
494 similar to those of a recent study of rectal masses treated with partial or complete pull-
495 through.[17] The median maximum tumor diameter in our study was 1.9cm (range, 1-6)
496 compared to 2.5cm (range, 1-10) in the study from Nucci et al.[17] This suggests a wide overlap
497 between tumors of similar size being treated with conservative submucosal resection in our
498 study and more aggressive pull-through in the study from Nucci et al[17] , which allows for
499 some comparison between the results.
500 In conclusion, submucosal resection via a transanal approach is a suitable technique for
501 resection of selected rectal masses. Morbidity is low and tumor-related death is possible but
502 uncommon for both benign and malignant tumors. Incomplete excision is associated with a
503 higher risk of recurrence and recurrence is a predictor for tumor-related death. Submucosal
504 resection of rectal carcinomas is associated with a good long-term outcome although survival
505 is significantly shorter than for benign masses. Recurrent benign or malignant masses can
506 benefit from repeat submucosal resection. Future prospective, randomized studies on larger
507 number of cases should focus on preoperative identification of which subset of patients might
508 be at higher risk of recurrence and tumor-related death, and may therefore, benefit from more
509 aggressive procedures, justifying the associated increase in morbidity. It is likely that
510 identifying pre-operative prognostic factors may require more refined staging and advanced

511 imaging. The role of MRI and/or ERUS to differentiate between early stage and advanced
512 stage rectal carcinoma in dogs should be investigated and might allow to channel individual
513 patients into the most appropriate treatment pathway.

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Author contributions:

Author 1: Study design and concept, data acquisition (case contribution: 26), analysis, and interpretation, primarily drafted and revised the work, accountable for all aspects of integrity and accuracy, and approved the published manuscript; Author 2: Study design, data acquisition (26), analysis, organization and interpretation, primarily drafted and revised the work, figures and tables preparation, accountable for all aspects of integrity and accuracy, and approved the published manuscript; Author 3: Study design, data acquisition (19), analysis, and interpretation, draft revision, and approved the published manuscript; Author 4: Study design, data acquisition (19), analysis, and interpretation, draft revision and approved the published manuscript; Author 5: Study design, data acquisition (8), analysis, and interpretation, draft revision and approved the published manuscript; Author 6: Study design, data acquisition (8), analysis, and interpretation, draft revision and approved the published manuscript; Author 7: Study design, data acquisition (8), analysis, and interpretation, draft revision and approved the published manuscript; Author 8: Study design and concept, data acquisition (2), analysis, and interpretation, draft revision, and approved the published manuscript; Author 9: Study design, data acquisition (1), analysis, and interpretation, draft revision and approved the published manuscript; Author 10: Study design, data acquisition and interpretation (21), statistical methods and analysis, primarily drafted and revised the manuscript, figures and tables preparation, accountable for all aspects of integrity and accuracy, and approved the published manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this report.

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634

635 **TABLES**
636

637 **Table 1.** 1-, 2-, 5- year disease free survival (DFS) for dogs with benign rectal neoplasia,
638 carcinoma in situ and rectal carcinoma treated by submucosa resection.

	Cases	1-year			2-year			5-year		
		Censored	Recurrence	Survival probability	Censored	Recurrence	Survival probability	Censored	Recurrence	Survival probability
Benign	48	8	3	94%	9	2	89%	15	1	85%
Carcinoma in situ	23	4	3	87%	2	2	76%	8	2	63%
Carcinoma	20	2	6	75%	4	0	75%	8	0	75%

639

Table 2. 1-, 2-, 5- year overall survival (OS) for dogs with benign rectal neoplasia, carcinoma in situ and rectal carcinoma treated by submucosa resection.

	Cases	1-year			2-year			5-year		
		Censored	Died	Survival probability	Censored	Died	Survival probability	Censored	Died	Survival probability
Benign	48	8	0	100%	12	1	98%	16	0	98%
Carcinoma in situ	23	4	0	100%	4	0	100%	10	3	80%
Rectal carcinoma	20	3	1	95%	4	1	89%	8	2	73%

646

647 **Table 3**. Simple logistic regression results determining factors associated with recurrence

648 after surgical intervention of rectal epithelial neoplasia in dogs

Logistic regression	**Rectal epithelial neoplasia survival**		
	OR[1]	95% CI[2]	*P* value
Size	*1.15*	*0.78-1.68*	*.467*
Distance from the anus	*0.94*	*0.68-1.29*	*.721*
Surgical time	***1.02***	***0.99-1.04***	***.069***
Diagnosis	***1.69***	***0.99-2.88***	***.051***
Margins	***2.15***	***0.81-5.70***	***.121***
Complications	***3.27***	***1.35-7.92***	***.008***

649 [1] OR: odds ratio; [2] 95% CI: ninety-five percent confidence interval: Reference category used

650 in logistic regression. Variables highlighted in bold qualified for inclusion in the multiple

651 regression analysis at $P < 0.20$ (Table 4)

652

653 **Table 4**. Multiple logistic regression results determining factors associated with recurrence
654 after surgical intervention of rectal epithelial neoplasia in dogs

Logistic regression	**Complications**		
	OR[1]	95% CI[2]	*P* value
Surgical time	1.00	0.98-1.03	.496
Diagnosis	1.08	0.56-2.07	.809
Margins	**2.97**	**1.16-7.62**	**.023**
Complications	**2.79**	**1.09-7.17**	**.032**

655 [1] OR = odds ratio [2] 95% CI = ninety-five percent confidence

656

657

658

659 **Table 5**. Simple logistic regression results determining factors associated with survival

660 time after surgical intervention of rectal epithelial neoplasia in dogs

Logistic regression	**Rectal epithelial neoplasia survival**		
	OR[1]	95% CI[2]	*P* value
Size	*1.01*	*0.55-1.86*	*.952*
Distance from the anus	*0.92*	*0.60-1.41*	*.704*
Surgical time	***1.04***	***1.01-1.07***	***.008***
Diagnosis	***3.62***	***1.49-8.80***	***.004***
Margins	***5.05***	***0.96-26.43***	***.055***
Complications	***2.76***	***0.79-9.54***	***.109***
Recurrences	***34.88***	***4.41-275.69***	***.001***

661 [1] OR: odds ratio; [2] 95% CI: ninety-five percent confidence interval: Reference category used

662 in logistic regression. Variables highlighted in bold qualified for inclusion in the multiple

663 regression analysis at $P < 0.20$ (Table 6)

664

665 **Table 6**. Multiple logistic regression results determining factors associated with survival
666 time after surgical intervention of rectal epithelial neoplasia in dogs

Logistic regression	**Complications**		
	OR[1]	95% CI[2]	*P* value
Surgical time	1.00	0.97-1.04	.721
Diagnosis	1.00	0.42-2.37	.991
Margins	4.89	0.92-25.81	.061
Complications	11.79	0.30-4.54	.811
Recurrences	**4.33**	**1.025-18.3**	**.046**

667 [1] OR = odds ratio [2] 95% CI = ninety-five percent confidence

668

FIGURES

Figure 1. Kaplan-Meier disease free survival curve for dogs with benign rectal neoplasia, carcinoma in situ and rectal carcinoma treated by submucosa resection.

675
676 **Figure 2.** Kaplan-Meier overall survival curve for dogs with benign rectal neoplasia,
677 carcinoma in situ and rectal carcinoma treated by submucosa resection.
678