Article

The effect of prednisone on histologic and gross characteristics in canine mast cell tumors

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Abstract — The objective of the study was to determine whether neoadjuvant prednisone therapy affects histological features of cutaneous and subcutaneous mast cell tumors. Twenty-eight dogs with a treatment naïve > 1-cm diameter mast cell tumor (MCT) were randomly assigned (Random number generator; Random.org, Dublin, Ireland) in a blinded fashion to receive either prednisone or placebo (Quality Food Center Pharmacy, Kirkland, Washington, USA). Volumes of mast cell tumors were calculated before incisional and excisional biopsies. Following incisional biopsy, patients received either prednisone (1 mg/kg body weight) daily or a placebo for 7 to 14 days leading up to excisional biopsy. Tumor grade for cutaneous MCT, and mitotic count and atypia for all tumors were reported. Perioperative treatment with prednisone had no significant effect on tumor grade, atypia, or mitotic count. Tumor volume was significantly decreased with prednisone treatment. The use of neoadjuvant prednisone to decrease MCT volume in order to facilitate tumor excision, can be considered without significant concern for change of tumor histologic features in the common population of low- to intermediate-grade MCT.

Résumé — Effet de la prednisone sur les caractéristiques histologiques et macroscopiques des mastocytomes canins. L'objectif de la présente étude était de déterminer si une thérapie néoadjuvante avec de la prednisone affecte les caractéristiques histologiques des mastocytomes cutanés et sous-cutanés. Vingt-huit chiens avec un mastocytome (MCT) ayant un diamètre > 1 cm avant le traitement furent répartis de manière aléatoire (Random number generator; Random.org, Dublin, Irlande) à l'aveugle pour recevoir soit de la prednisone ou un placebo (Quality Food Center Phamacy, Kirkland, Washington, USA). Les volumes des MCT furent calculés avant les biopsies d'incision et d'excision. À la suite des biopsies d'incision, les patients reçurent soit de la prednisone (1 mg/kg de poids corporel) quotidiennement ou un placebo pour 7 à 14 jours menant à la biopsie d'excision. Le grade des tumeurs pour les MCT cutanés, ainsi que le dénombrement mitotique et l'atypie pour toutes les tumeurs furent rapportés. Le traitement préopératoire avec de la prednisone n'a pas eu d'effet significatif sur le grade des tumeurs, l'atypie ou le dénombrement mitotique. Le volume des tumeurs était réduit significativement avec le traitement à la prednisone. L'utilisation néoadjuvant de prednisone afin de diminuer le volume des MCT dans le but de faciliter l'excision des tumeurs peut être considérée sans préoccupation significative pour des changements dans les caractéristiques histologiques des populations habituelles de MCT de grade bas à intermédiaire.

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Introduction

Mast cell tumors (MCT) are the most common malignant cutaneous tumor in dogs, and are typically diagnosed based on fine-needle aspiration and cytologic evaluation (1). Prognostic indicators include: histologic grade, clinical stage, tumor location, proliferation indices [e.g., mitotic count, agrophilic nucleolar organizer regions (AgNOR) scoring, Ki67 and/or proliferating cell nuclear antigen (PCNA) labeling index], presence of systemic signs, as well as c-Kit receptor localization and mutation status (2–9).

Surgical excision is the mainstay of treatment for localized canine MCT, with risk for local tumor recurrence depending on the completeness of surgical excision and tumor grade (9–11). For low- and intermediate-grade tumors (Patnaik grading system) with complete excision, the chance of recurrence has been reported as low as 5% to 11% (9,12), whereas high-grade

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tumors (Patnaik, Kiupel grading systems) have a 35.9% chance of recurrence with complete excision (11). Recurrence rates following incomplete excision or excision with margins of < 2 mm were 6% to 30% for low- and intermediate-grade MCTs, compared to 85% to 90% for high-grade MCTs with incomplete margins (9,13,14). For high-grade tumors, larger tumors, and those in locations in which wide margins are not attainable, neoadjuvant treatment with corticosteroids is often applied in an effort to reduce peritumoral edema and potentially down-stage local disease with the goal to facilitate complete excision (15). Corticosteroids have been demonstrated to inhibit MCT proliferation *in vitro,* perhaps have a direct anticancer effect due to the presence of glucocorticoid receptors on the tumor cell itself (16), and/or lessening of peritumoral edema and inflammation (17). Of concern is whether the use of preoperative corticosteroids may alter the histological grade or other microscopic features of the tumor. A change in such could lead to incorrect prognostication and potentially inappropriate treatment decisions following surgery, resulting in either under- or over-treatment in the adjuvant setting.

The aim of this study was to answer the question whether neoadjuvant prednisone therapy affects tumor grade, in the case of cutaneous MCT, or other histological prognostic features of both cutaneous and subcutaneous MCT. The null hypothesis was that treatment with prednisone for 7 to 14 d before excisional biopsy would not have a statistically significant effect on MCT grade, cellular atypia, or mitotic count.

Materials and methods

Patient selection

Client-owned dogs of any age, breed, or gender with a newly diagnosed, treatment naïve MCT of greater than 1 cm diameter were eligible for enrollment. Any dog which had a recurrent MCT, or which had received a corticosteroid, non-steroidal anti-inflammatory drug (NSAID) or chemotherapeutic agent within the past 7 d was excluded. Tumor volume was determined before manipulation by measuring and calculating the volume of an ellipsoid [$4/3\pi$ (0.5 length $\times$ 0.5 width $\times$ 0.5 depth)]. Informed consent was obtained from all dog owners before enrollment in the study, and all surgical procedures were performed at Seattle Veterinary Specialists-Blue Pearl.

Incisional biopsy

Prior to randomization, patients underwent incisional biopsy obtained on day 0. The incisional biopsy was performed using a standard pretreatment protocol with diphenhydramine (Diphenhydramine HCL; Armas Pharmaceuticals, Manalapan, New Jersey, USA), 2 mg/kg body weight (BW), IM, once, famotidine (Famotidine Injection; West-Ward Pharmaceuticals, Eatontown, New Jersey, USA), 1 mg/kg BW, IV, once, opioid [(oxymorphone, Opana; Endo Pharmaceuticals, Malvern, Pennsylvania, USA), hydromorphone (Hydromorphone HCl; Acorn, Lake Forest, Illinois, USA), or methadone (Methadone HCl; Mylan Institutional, Rockford, Illinois, USA), 0.1 to 0.2 mg/kg BW, IM, once], IV catheter placement, diazepam (Diazepam Injection; Hospira, Lake Forest, Illinois, USA), 0.1 to 0.2 mg/kg BW, IV, at induction, and propofol (Propoflo; Zoetis, Kalamazoo, Michigan, USA) titrated to effect. An incisional biopsy was taken from the center of the lesion using a 4- to 6-mm punch. The biopsy defect was then sutured using monofilament nylon suture. The tumor sections stained with standard hematoxylin and eosin (H&E) stain were reviewed by a single, blinded pathologist, and tumor grade (Patnaik and Kiupel) and the mitotic counts (derived from counting mitotic figures in 10 consecutive high power fields) were determined.

Treatment

The dogs were randomly assigned to a treatment or placebo group (A). Following the incisional biopsy, dogs were given a cellulose placebo (B) or prednisone (Prednisone; Jubilant Cadista Pharmaceuticals, Salisbury, Maryland, USA), 1 mg/kg BW, PO, q24h, as well as famotidine, 1 mg/kg BW, PO, q24h, and diphenhydramine, 2 mg/kg BW, PO, q12h, for 7 to 14 d before the definitive excisional biopsy. Tramadol (Tramadol HCl; Amneal Pharmaceuticals, Brookhaven, New York), 2 to 4 mg/kg BW, q8h to 12h, was also prescribed as needed for pain control for 5 d after the incisional biopsy. Prednisone was dispensed in 5 mg capsules only and each placebo capsule was treated as an equivalent to 5 mg of prednisone for dosing uniformity. Dosing was based on a 1 mg/kg BW, PO, q24h oral prednisone equivalent. Treatment was continued for 7 to 14 d until the excisional biopsy.

Excisional biopsy

Prior to manipulation, the post-treatment tumor volume was measured and recorded. The excisional biopsy was performed using a standard pretreatment with diphenhydramine (Armas Pharmaceuticals), 2 mg/kg BW, IM, once; famotidine (West-Ward Pharmaceuticals), 1 mg/kg BW, IV, once; opioid [hydromorphone (Acorn), methadone (Mylan Institutional)], 0.1 to 0.2 mg/kg BW, IM, once, IV catheter placement, diazepam (Hospira), 0.1 to 0.2 mg/kg BW, IV at induction, and propofol (Zoetis) titrated to effect to facilitate intubation. The dogs were maintained on isofluorane gas anesthetic in oxygen. Tumors were then excised using a proportional-margins approach (18) with margins measured in cm and marked using a sterile ink pen in surgery. Tumors larger than 3 cm in diameter were excised with 3 cm margins. The tissue margins were inked at the time of surgery in each orientation before placement in formalin. Closure was routine and performed according to surgeon preference. Prednisone was discontinued at the time of excisional biopsy and all dogs were re-examined 2 wk after surgery by the principal investigators.

Blinding

Principal investigators, surgeons, and the pathologist were blinded to treatment status until completion of the study. One surgery technician was aware of the treatment status and dispensed the medication.

Histopathology

All slides were evaluated by a single Board-certified anatomic pathologist (AB). Tumor grade was reported for cutaneous MCT based on the Patnaik (3-tiered) system (19) and the

Table 1. Fisher's exact test *P*-values for prednisone treatment and placebo groups.

Variable	Categories	Prednisone	Placebo	Fisher's *P*-value
Gender	female, male	13, 5	7, 6	0.45
Status	intact, neuter, spay	1, 5, 12	1, 5, 7	0.85
Tumor site	cutaneous, subcutaneous	13, 5	9, 4	1.00
Margins[a]	complete, incomplete	14, 4	11, 2	1.00
Pre-treatment Grade[b] (cutaneous MCT)	I, II, III	1, 11, 0	1, 8, 0	1.00
Pre-treatment Grade (cutaneous MCT)	low, high	12, 0	9, 0	—
Post-treatment Grade (cutaneous MCT)	I, II, III	3, 10, 0	0, 9, 0	0.78
Post-treatment Grade (cutaneous MCT)	low, high	13, 0	7, 2	0.56
Pre-treatment atypia[c]	1, 2, 3	5, 7, 3	4, 6, 3	1.00
Post-treatment atypia	1, 2, 3	5, 5, 5	4, 6, 3	0.66

[a] Margins were complete if they were ≥ 1 mm.
[b] Tumor grade was Patnaik (I, II, III) and Kiupel (low, high).
[c] Atypia was categorized as 1 (mild), 2 (mild to moderate), 3 (moderate).

Kiupel (2-tiered) grading system (20). Mitotic count and cellular atypia were also reported. Atypia was reported as mild, mild to moderate, and moderate. Atypia and mitotic count were reported for subcutaneous MCT since traditional grading does not apply to subcutaneous MCT. Excisional biopsy margins were reported for all tumors, with complete (histological) margins considered to be ≥ 1 mm.

Statistical analyses

A sample size power calculation performed *a priori* and based on a paired *t*-test and alpha = 0.05 ($P < 0.05$), beta = 0.20 (Power = 80%), a difference to detect = 25%, and a standard deviation of the differences = 1.5, yielded an estimate of 15 dogs per group. Wilcoxon rank-sum test was used to assess differences between the treatment groups using the variables of age, weight, treatment duration, pre-treatment tumor volume, post-treatment tumor volume, pre-treatment mitotic count, and post-treatment mitotic count.

Wilcoxon signed-rank test was used to assess differences between tumor volumes and tumor mitotic count pre- and post-treatment within a treatment group. Chi-square test and Fischer's exact test were used to assess differences between the treatment groups with respect to gender, castration status, pre-treatment tumor grade, post-treatment tumor grade, pre-treatment tumor atypia, post-treatment tumor atypia, tumor site (subcutaneous *versus* cutaneous), and margins. McNemar's test was used to assess change of tumor grade, mitotic count, and atypia within a group pre- and post-treatment. Wilcoxon rank-sum test was used to assess the change of tumor grade, mitotic count, and atypia between the groups. Atypia was scored as 1 (mild), 2 (mild to moderate), and 3 (moderate) for statistical analysis.

Results

Twenty-eight client-owned dogs, 18 females and 10 males, were enrolled in the study. The breeds included boxer, Boston terrier, pug, border collie, Labrador retriever, poodle, dachshund, Italian greyhound, and miniature schnauzer. The treatment group consisted of 16 dogs (11 females, 5 males) with a median age of 9.9 y (range: 5.5 to 23.5 y), and a median weight of 11 kg (range: 4.8 to 41.4 kg). The placebo group consisted of 12 dogs (7 females, 5 males) with a median age of 9.5 y (range: 7 to 13.5 y) and a median weight of 19.5 kg (range: 7.4 to 51.9 kg). The placebo group dogs weighed significantly more ($P < 0.05$) than the treatment group dogs. There were 18 MCT (13 cutaneous, 5 subcutaneous) in the treatment group and 13 MCT (9 cutaneous, 4 subcutaneous) in the placebo group (Table 1). Pre-treatment tumor grade, tumor volume, and atypia were not significantly different between the groups. There was a significant difference in the pre-treatment mitotic count between the treatment groups ($P = 0.04$). The median mitotic count of the treatment group was 0 (range: 0 to 3), while the median mitotic count for the placebo group was 1 (range: 0 to 4). Of the 13 cutaneous MCT incisional biopsies in the treatment group, there were 11 Grade II tumors, and 1 Grade I tumor when graded by the Patnaik system; one incisional biopsy did not yield an MCT. When graded by the Kiupel system all 13 cutaneous tumors were low grade. In the placebo group, the 9 cutaneous tumor incisional biopsies yielded 8 Grade II tumors and 1 Grade I tumor when graded by the Patnaik system, and all were low grade according to the Kiupel system.

The duration of treatment ranged from 7 to 14 d. The median treatment duration for the treatment group was 8 d (range: 7 to 12 d), and was not significantly different from the

Table 2. Wilcoxon rank-sum test *P*-values for non-categorical variables for prednisone and placebo groups.

	Prednisone			Placebo			Wilcoxon rank-sum test
Variable	Median	Q1	Q3	Median	Q1	Q3	*P*-value
Age (years)	9.9	8.2	10.3	9.5	7.9	11.9	0.94
Weight (kg)	11.0	7.9	27.9	28.0	19.5	31.2	0.05
Treatment duration (days)	8.0	7.3	10.8	7.0	7.0	8.0	0.21
Pre-treatment volume (cm^3)	6.2	1.4	10.5	14.1	4.4	37.7	0.11
Post-treatment volume (cm^3)	2.3	0.9	7.3	14.1	5.2	23.8	0.03
Pre-treatment mitotic count	0.0	0.0	1.0	1.0	0.0	3.0	0.04
Post-treatment mitotic count	0.0	0.0	1.0	1.0	0.0	2.0	0.12

Data were summarized by means of the median, Q1, and Q3 (50th, 25th, and 75th percentiles, respectively).

Table 3. Comparison of pre-treatment and post-treatment tumor volumes and tumor counts for the prednisone treated and placebo groups.

	Pre-treatment			Post-treatment			Wilcoxon rank-sum test
Variable	Median	Q1	Q3	Median	Q1	Q3	*P*-value
Prednisone volume (cm^3)	6.2	1.4	10.5	2.3	0.9	7.3	0.01
Placebo volume (cm^3)	14.1	4.4	37.7	14.1	5.2	23.8	0.59
Prednisone mitotic count	0.0	0.0	1.0	0.0	0.0	1.0	0.43
Placebo mitotic count	1.0	0.0	3.0	1.0	0.0	2.0	0.48

Data were summarized by means of the Median, Q1, and Q3 (50th, 25th, and 75th percentiles, respectively). The Wilcoxon signed-rank test *P*-value is reported.

median treatment duration of the control group, which was 7 d (range: 7 to 14 d) ($P = 0.2$).

Excisional biopsy tumor grade, atypia and mitotic count did not change significantly from incisional biopsy indices with either prednisone or placebo, and there remained no difference between groups. In the treatment group, 2/13 tumors changed grade from II to I, when graded by the Patnaik system, whereas 0/13 tumors changed grade based on the Kiupel system. In the placebo group 0/9 tumors changed grade with Patnaik grading; however, 2/9 tumors changed from low to high grade with the Kiupel grading. There was no significant difference in change of tumor grade between the groups ($P = 0.11$). In the treatment group mitotic count changed in 11/17 tumors, with the mitotic count decreasing in 6 tumors and increasing in 5 tumors. In the placebo group, mitotic count changed in 9/13 tumors with the mitotic count decreasing in 5 tumors, and increasing in 4 tumors, and remaining unchanged in 4 tumors. There was no significant difference between the groups with respect to mitotic count changes ($P = 0.9$). In the treatment group, cellular atypia changed in 5/17 tumors (atypia score decreasing in 3 tumors and increasing in 2 tumors), and in the placebo group cellular atypia changed in 4/13 tumors (atypia score decreasing in 2 tumors and increasing in 2 tumors). There was no significant difference between the groups with respect to cellular atypia changes ($P = 0.9$).

Tumor volume was significantly ($P = 0.01$) decreased with prednisone treatment (Tables 2, 3). The median tumor volumes in the treatment group before and after treatment were 6.2 cm^3 (range: 0.5 to 65.5 cm^3) and 2.3 cm^3 (range: 0.5 to 54.6 cm^3), respectively, representing a median 3.9 cm^3 or 63% decrease in tumor volume: 8 tumors stable disease, 8 tumors partial response, and 2 tumors progressive disease. Tumor volume in the control group was not significantly different between pre-treatment and post-treatment, with a pretreatment median of 4.4 cm^3 (range: 0.3 to 78.6 cm^3) and post-treatment median of 5.2 cm^3 (range: 0.4 to 54.6 cm^3). Four tumors showed progressive disease, 6 tumors partial response, and 3 tumors stable disease.

In the treatment group there were 14/18 tumors excised with complete margins and 4/18 excised with incomplete margins, compared to the control group in which 11/13 tumors were excised with complete margins and 2/13 tumors were excised with incomplete margins. The percentage of tumors with incomplete margins was not significantly different between the groups.

Complications following excisional biopsy occurred in 2 dogs. One dog in the treatment group developed a seroma which resolved with drainage and 1 dog in the control group had incisional dehiscence which healed by second intention with open wound management.

Discussion

Neoadjuvant treatment of MCT with a glucocorticoid is often applied to reduce peri-tumoral edema and potentially down-stage local disease, in order to facilitate complete tumor excision. The administration of a glucocorticoid has been demonstrated to result in a reduction in grossly measured MCT volume (15,21,22). Stancliff et al (15) reported a reduction in tumor volume of 25% or more, with a median 81% reduction in 87% of prospectively treated grade II MCTs. Responses, however, were not durable and typically lasted only weeks (15). Matsuda et al (16) showed that glucocorticoids suppress MCT proliferation both *in vitro* and *in vivo,* and that MCT sensitivity

to glucocorticoids was significantly correlated with glucocorticoid receptor expression. This response is dependent on the level of tumor cell differentiation, with poorly differentiated, higher grade tumors responding less effectively (17).

The response of MCT to corticosteroids has been shown to be both dose dependent (17) and time dependent (21). However, Stancliff et al (15) showed that doses between 1 mg/kg BW and 2.2 mg/kg BW appear to achieve significant reductions in tumor volume, with no significant difference in response between 1 and 2.2 mg/kg BW per day dosing. For this study, a dose of 1 mg/kg BW per day was chosen because it has been demonstrated to reduce mast cell tumor volume without producing as many undesirable side effects which are often present at higher doses. The treatment duration of 7 to 14 d was chosen because the investigators felt it would give adequate time for tumor response without delaying standard of care treatment for client-owned animals. Previous reports have shown a 70% response with a median treatment duration of 9 d (15). Teng et al (21) showed that median time to maximum tumor regression was 14 d, with 81.5% of patients reaching maximum regression by 21 d. The method of incisional biopsy using a biopsy punch was chosen as it has been demonstrated to be an accurate method of sampling MCT (100% Patnaik, 95% Kiupel) compared with excisional biopsy (23). However, there were 2 incisional biopsies in our study that did not yield MCT. This may have occurred due to localized inflammation or error in biopsy technique.

Measurement outcomes in this study included tumor grade when appropriate and mitotic count because these are the commonly reported prognostic factors for MCT biopsy in clinical practice (24). Tumor grade and mitotic count are important independent prognostic factors (4,5), and in this study neoadjuvant treatment with prednisone did not affect tumor grade, or mitotic count. This finding may reflect a lack of sensitivity of the histopathological analysis performed on MCT biopsy samples, or it is possible that other histological features could be affected by neoadjuvant prednisone therapy. Veterinary studies have shown that neoadjuvant prednisone has the ability to alter the expression of certain mast cell growth factors, including c-Kit (21). Aberrant c-Kit expression has been associated with poorer clinical outcome, and previous studies have shown that 15% to 40% of all canine MCTs are affected by c-Kit mutations leading to aberrant expression (25). The combination of Ki67 and proliferating cell nuclear antigen scores has been shown to be prognostic for local recurrence, and dogs with such recurrence had significantly decreased survival times (9). Furthermore, prednisolone affects Kit pattern staining and Kit pattern staining correlates with response to prednisolone (21). It was beyond the scope of the current study to evaluate immunohistochemical features, such as Ki-67, and c-Kit (6,8,13,26,27); however, it may be important to consider the effects of prednisone on these prognostic markers with future studies. In our study, there was no difference between the treatment and placebo groups with respect to incomplete margins. This suggests that using reduced tumor size to determine excisional margins after prednisone treatment does not statistically increase the risk of incomplete excision.

There are several limitations in this study. The largest potential confounding factor of this study was that both cutaneous and subcutaneous MCT were included. The traditional Patnaik and Kiupel grading schemes were not developed for subcutaneous tumors; however, in the absence of an alternative grading system many pathologists still grade subcutaneous tumors based on the traditional systems, and many oncologists still extrapolate these grading schemes to include subcutaneous MCT when making treatment decisions in clinical practice. Although the application of traditional grading schemes has not been clearly shown to be of prognostic utility, there is an impression that mitotic count, when applied to subcutaneous MCT, does provide prognostic information similar to cutaneous MCT (7). We chose to include subcutaneous MCT in this study because they are common, and differentiating subcutaneous MCT from cutaneous MCT based strictly on gross features can be difficult.

The second limitation is the lack of high-grade tumors in this study. Most tumors (93%) were Grade II (Patnaik) or low grade (Kiupel), and higher-grade tumors may respond differently to prednisone (28). As high-grade tumors are statistically less common (3% to 21%) (24), we felt this distribution reflected a common distribution from the population. Based on our data we cannot conclude with certainty that prednisone would not alter histological features in high-grade MCT.

We attempted to minimize the confounding effect of tumor grading subjectivity (29) by having a single pathologist perform all the histopathology. As previously described, the use of c-Kit, AgNOR, and Ki-67 may improve our ability to predict biological behavior and may be the focus of a future study.

The use of other pharmaceuticals (famotidine, diphenhydramine, opioids) in conjunction with the prednisone potentially could have impacted tumor grade, although there are no published data to support this possibility. Since both treatment groups received identical adjunctive treatments, any changes in tumor grade should have been equivalent between the 2 groups. A final limitation of this study was the small sample size, which could lead to a type II error with regard to the effect of prednisone treatment. Twenty-eight patients were included in the study, with 2 of the incisional biopsies returned as nondiagnostic. The criteria for power calculation used for this study were based on a paired *t*-test and alpha = 0.05 ($P < 0.05$), beta = 0.20 (Power = 80%), a difference to detect = 25%, and a standard deviation of the differences = 1.5, yielding an estimate of 15 dogs per group.

This study tested the hypothesis in a randomized, double-blinded fashion, whether neoadjuvant prednisone therapy statistically affects tumor grade, atypia, or mitotic count. We accept the null hypothesis, that treatment with prednisone for 7 to 14 d before excisional biopsy does not have a statistically significant effect on MCT grade, atypia, or mitotic count in low to intermediate grade MCT. Furthermore, we recognize that neoadjuvant prednisone administration can result in a significant decrease in tumor volume without a significant increase in postoperative incisional complications or incomplete margins. In conclusion, the use of neoadjuvant prednisone to decrease MCT volume in order to facilitate tumor excision can be considered without significant concern for change of tumor histologic

features, and thus prognostication in low to intermediate grade MCT. Ideally, future studies will include additional prognostic markers (c-Kit, Ki67, AgNOR, and PCNA), and longer-term follow-up for tumor recurrence and high-grade MCT.

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