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Outcome and Prognostic Factors Following Adjuvant Prednisone/Vinblastine Chemotherapy for High-Risk Canine Mast Cell Tumour: 61 Cases

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ABSTRACT. The medical records of 61 dogs with MCT at high risk for metastasis that were treated with prednisone and VBL following excision +/– radiation therapy were reviewed, and median disease-free interval (DFI), median overall survival time (OS) and prognostic factors assessed. Adverse effects, mostly mild, were noted in 26% of patients, usually after the first VBL dose. 6.5% experienced severe neutropenia. The DFI was 1305 days, and the OS was not reached, with 65% alive at 3 years. 100% of dogs with "high-risk" grade II MCT were alive at 3 years. The OS for dogs with grade III MCT was 1374 days. Histologic grade, location (mucous membrane vs. skin) and use of prophylactic nodal irradiation predicted outcome. Prednisone and VBL chemotherapy is well tolerated, and results in good outcomes following surgery in dogs with MCT at high risk for metastasis. High-grade and mucocutaneous tumors had a worse outcome, and the use of prophylactic nodal irradiation appeared to improve outcome in this group of dogs.
KEY WORDS: canine, mastocytoma, Prednisone, vinblastine.

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Mast cell tumour (MCT) represents the most common malignant cutaneous tumour in the dog [29]. High-grade or undifferentiated MCT (Patnaik grade III) comprise 29 to 40% of all MCT [2, 14, 22]. In addition to local infiltration, they have a reported metastatic rate of 55 to 96%, and are more likely to result in tumor-related death than are low- or intermediate-grade MCT [29]. While some discordance exists in the literature, patients with MCT of any grade involving the regional lymph node (LN) or arising from a mucous membrane (e.g. gingiva, perineum, prepuce, nail-bed) may also be at higher risk for eventual death from MCT [1, 10, 28–30]. Thus, local therapies alone may be suboptimal for tumour control in these patients.

Survival times after surgery alone for high-grade MCT were reported in early studies as 15% at seven months, 6% at 48 months, and a median survival time (MST) of 13 weeks [2, 3, 22]. More recent studies have reported a MST of approximately 9 months with resection alone in dogs with high-grade MCT [20, 25].

Several studies have evaluated chemotherapy for the treatment of measurable MCT, and response rates from 7% to 78% have been documented [8, 10, 17, 18, 23, 28]. However, few studies have evaluated the efficacy of chemotherapy as adjuvant treatment for MCT [7, 28].

Vinblastine (VBL) is an antimicrotubule alkaloid used in the treatment of hemolymphatic neoplasia in dogs [12], and various human malignancies [24]. We previously reported the results of a study employing prednisone/VBL for the treatment of dogs with gross, microscopic and "high-risk" MCT. An objective response rate of 44% was reported in dogs with gross disease, and there was suggestion that dogs receiving prednisone/VBL following surgery had a favorable clinical outcome compared with historical controls receiving local therapy alone [28]. However, the clinical characteristics of these patients were variable, and a relatively small number were treated in the surgical adjuvant setting. A second study employing postoperative prednisone/VBL was reported recently [7]. The vast majority of tumours treated were incompletely resected intermediate-grade cutaneous tumours at low risk for metastasis. Recurrence and metastasis were encouragingly rare events, however.

The goal of this study was to retrospectively evaluate a larger, more uniform cohort of canine MCT patients at high risk for metastasis treated in the adjuvant setting with prednisone/VBL chemotherapy.

MATERIALS AND METHODS

Patient selection: A search of the University of Wisconsin—Madison Veterinary Medical Teaching Hospital (UW-MVMTH) database identified dogs with MCT receiving prednisone/VBL. Inclusion criteria were the absence of severe concurrent disease, no concurrent systemic antineoplastic therapy other than prednisone and VBL, complete staging, and absence of measurable disease following surgery. To be considered at "high risk" for metastasis, patients had a tumour histologically interpreted as "high grade", or had an intermediate-grade tumour occurring at a mucocutaneous junction or with histologic or cytologic evidence of LN metastasis. All patients underwent clinical staging, consisting of physical examination, complete blood count, serum biochemistry profile, abdominal ultrasound, and palpation +/– needle aspiration cytology of the regional LN. Lymph nodes were considered positive for metastasis if they contained sheets or clusters of mast cells: occasional

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scattered individual mast cells were not sufficient for a diagnosis of LN metastasis.

Patients were divided into 2 populations based on the adequacy of local tumour control. Microscopic disease was defined as the absence of measurable tumour but histological evidence of tumour cells extending to the margins of surgical excision. Adequate local therapy (ALT) was defined as "appropriately aggressive" surgery with no histological evidence of tumour cells at the surgical margin, or marginal excision followed by radiation therapy (RT).

The RT consisted of either 15 daily 3.2 Gray (Gy) treatments given over three consecutive weeks (M-F) to a total dose of 48 Gy, or four once-weekly 8 Gy treatments given to a total dose of 32 Gy, calculated using source to axis distance technique. When appropriate, blocks were used to spare critical underlying tissues, and wedges were used to improve homogeneity of dose distribution. The RT treatments were performed using a ^{60}Co teletherapy unit (Theratron 780, Atomic Energy of Canada Ltd.), with 0.5 cm tissue-equivalent bolus material over skin incisions. Treatment fields included 3-cm margins around surgical scars. In some patients, regional LN cytologically free of metastatic disease were prophylactically irradiated using a protocol identical to that applied to the primary site, without bolus application.

Chemotherapy administration: Prednisone was administered orally at an initial dose of 2 mg/kg daily, and was tapered and discontinued over 12 to 26 weeks. Vinblastine was given as a rapid intravenous bolus at 2 mg/m^2 every 1–2 weeks. Chemotherapy was generally initiated within 2 weeks of surgery, and was administered concurrent with RT, if used. All dogs were scheduled to receive weekly VBL treatments for 4 weeks, followed by four biweekly treatments. Fifty-nine of 61 patients received the protocol as scheduled while 2 patients received every-other-week VBL injections for a total of 6 or 12 treatments. Complete blood counts were performed and clients questioned regarding adverse events prior to each treatment. Adverse events were graded using the Veterinary Co-operative Oncology Group—Common Terminology Criteria for Adverse Events [31].

Patient assessment: Follow-up information was obtained through recheck examinations at the UW-MVMTH, or through telephone communication with the referring veterinarians and/or owners. Although recheck evaluation procedure was not standardized, examinations at the time of recheck typically included palpation of the primary site and regional LN, aspiration of that LN if palpably enlarged, and abdominal ultrasound. Any new masses were evaluated cytologically. Disease-free interval (DFI) was defined as the time interval between the initiation of chemotherapy and the development of local recurrence, metastasis or new MCT. Overall survival (OS) was defined as the time interval between the initiation of chemotherapy and death.

Statistical analysis: Variables assessed for value as predictors of OS and DFI included age, sex, number of cutaneous tumours (one vs. multiple), LN status, locally recurrent tumour at time of treatment initiation, location (mucous membrane vs. other), histologic grade, local therapy type, concurrent RT, RT protocol used (weekly vs. daily) and use of prophylactic LN irradiation (PNI). These variables were selected based on previous reports and anecdotal evidence. The DFI and OS in each group were calculated using the Kaplan-Meier product limit method [15]. Differences in DFI and OS between dogs grouped in different covariates were analyzed using the generalized Wilcoxon test [4]. This was then followed by a multivariate model in which significant variables identified in the univariate model were included [6]. Differences in categorical data between groups (e.g. use of PNI or adequacy of local control) as related to outcome (recurrence, metastasis) were compared using Fisher's exact test. Statistical calculations were performed using commercial statistical software packages.[a,b] A p value of 0.05 was considered significant for all statistical analyses.

RESULTS

Sixty-one dogs met the criteria for inclusion (Table 1), 23 of which were reported in a previous study [28]. Additional follow-up was obtained on the patients reported previously. No dogs had received prior cytotoxic chemotherapy, but 4 had received prior systemic corticosteroid therapy. Ten dogs were classified as having microscopic disease, and 51 as having received ALT. Lymph node metastasis was documented in 28 patients, and LN excision was performed in all prior to the initiation of chemotherapy. Fourteen dogs had a history of having had more than one cutaneous tumour at presentation, 11 had tumours arising from a mucous membrane (vulva, prepuce, conjunctiva, oral cavity) and 10 had a history of local recurrence prior to treatment initiation. Fourteen patients had intermediately differentiated (Grade II) MCT, and 47 had poorly differentiated (Grade III)

Table 1. Patient characteristics

Age (yrs) Median (range)		9 (2–14)
Weight (kg) Median (range)		26 (4.5–66)
Sex:		
	Spayed Female	34
	Castrated Male	23
	Intact Male	4
Breed:		
	Labrador Retriever	11
	Mixed Breed	9
	Golden Retriever	3
	Australian Shepherd	2
	Viszla	2
	Akita	2
	Poodle	2
	German Shepherd	2
	Bernese Mountain Dog	2
	Schnauzer	2
	Gordon Setter	2
	Springer Spaniel	2
	West Highland White Terr	2
	Other (1 each)	18

tumours. Of the intermediate-grade tumours, 12 were node-positive, and three arose from mucous membranes.

Adverse effects were noted in 16/61 (26%) of patients, usually after the first dose of VBL. These were considered mild in 12 patients, and severe in 4. Mild side effects not requiring specific therapy included grade 1, self-limiting vomiting in six patients, grade 2 neutropenia without evidence of sepsis in 4, grade 1 diarrhea in 5, grade 2 anorexia in 2, and lethargy in one. Three dogs had dose reductions as a result of these effects. Grade 3 or 4 neutropenia (neutrophils less than 1000/μL) with fever, necessitating hospitalization, occurred in 4 patients. This led to treatment discontinuation in 2 patients (however, these 2 dogs were included in survival and DFI analysis), a dose reduction in one, and fatal sepsis in one. However, the owner of the dog that died declined hospitalization for treatment.

There was no statistical difference in outcome between dogs with microscopic local disease and dogs receiving ALT. Among the dogs receiving ALT, 15 underwent wide-margin surgery with clean histological margins, and 36 received RT following incomplete surgical excision in conjunction with prednisone/VBL. Ten patients received 48 Gy, and 26 received 32 Gy. There was no statistical difference in outcome based on use of RT versus wide-margin surgery, or type of RT protocol employed. Of the patients receiving RT, 26 patients received PNI and 10 patients did not. There was a trend toward improved DFI (p=0.082) and OS (p=0.0536) favoring the dogs receiving PNI, when comparing these groups. However, when the group of dogs receiving PNI was compared with all other dogs, regardless of whether they received RT to their primary site, there was a statistically significant improvement in both DFI and OS (Fig. 1, Tables 2 and 3).

Twenty patients received additional therapy after having failed prednisone/VBL, including surgery (n=12), RT (n=3), and medical therapy (n=12) (additional prednisone/VBL, asparaginase, lomustine, vinorelbine, prednisone alone, dolastatin-10 [27] or genetically modified *Salmonella* [26]). Several dogs received more than one additional form of treatment.

Of the study population, 43 patients were censored from survival analysis for the following reasons: Alive without evidence of disease (n=21), dead due to unrelated causes (n=18), lost to follow-up with disease (n=3) or lost to follow-up without evidence of disease (n=1). Median duration of follow-up on censored patients was 650 days. Thirty-six patients were also censored from DFI analysis for similar reasons.

The median DFI for all treated patients was 1305 days, and the median censored OS was not reached, with 80%, 70% and 65% alive at one, 2 and 3 years following treatment initiation. Upon univariate analysis, histologic grade, location and use of PNI were significant predictors of OS (Figs. 1 and 2, Table 2). Identical factors were significant for predicting time to DFI (Figs. 1 and 2, Table 3).

Twenty-four of 61 patients (39%) developed MCT progression. Recurrence at the surgery site occurred in 7 (11.5%) patients (3 of which received RT), and 9 (14.8%) developed metastasis (8 to regional LN and one to spleen). Two dogs receiving 32 Gy PNI developed metastasis to the irradiated LN. Eleven dogs (18%) developed additional cutaneous MCT at distant, unrelated sites. Location of disease progression was not recorded in 4. There was no statistical correlation between the likelihood of local or LN failure and the adequacy of local control (microscopic vs. ALT) or the utilization of PNI. History of multiple cutaneous MCT did not correlate with development of another cutaneous MCT subsequent to prednisone/VBL.

When all variables correlated with outcome upon univariate analysis were subjected to a multivariate model, histologic grade remained a significant predictor of DFI, however none of the identified variables predicted OS.

Given the marked difference in outcome between "high-risk" intermediate-grade and high-grade MCT in this study,

Table 2. Univariate analysis of prognostic variables for effect on disease-free interval for 61 dogs with high risk mast cell tumor treated with prednisone and vinblastine

Variable	Number of dogs	Median DFI	p Value[a]	1YDF[b]	2YDF[c]	3YDF[d]
Histologic Grade						
III	47	538 d[e]		55%	45%	41%
II	14	NR[f]	0.0031	93%	93%	93%
Location						
Muc. Membrane	11	222 d		25%	25%	25%
Skin	50	NR	0.0056	74%	64%	60%
PNI[g]						
No	35	757 d		56%	49%	43%
Yes	26	NR	0.0371	80%	71%	71%

a) *P* values were calculated with the generalized Wilcoxon test.
b) 1YDF = One-year disease-free percentage.
c) 2YDF = Two-year disease-free percentage.
d) 3YDF = Three-year disease-free percentage.
e) d = Days.
f) NR = Median not reached.
g) PNI = Prophylactic lymph node irradiation.

Table 3. Univariate analysis of prognostic variables for effect on overall survival for 61 dogs with high risk mast cell tumor treated with prednisone and vinblastine

Variable	Number of dogs	Median OS	p Value[a)]	1YS[b)]	2YS[c)]	3YS[d)]
Histologic Grade						
III	47	1374 d[e)]		70%	58%	53%
II	14	NR[f)]	0.0041	100%	100%	100%
Location						
Muc. Membrane	11	326 d		44%	30%	30%
Skin	50	NR	0.0090	83%	75%	71%
PNI[g)]						
No	35	1374 d		70%	58%	58%
Yes	26	NR	0.0205	96%	87%	78%

a) *P* values were calculated with the generalized Wilcoxon test.
b) 1YS = One-year survival percentage.
c) 2YS = Two-year survival percentage.
d) 3YS = Three-year survival percentage.
e) d = Days.
f) NR = Median not reached.
g) PNI = Prophylactic lymph node irradiation.

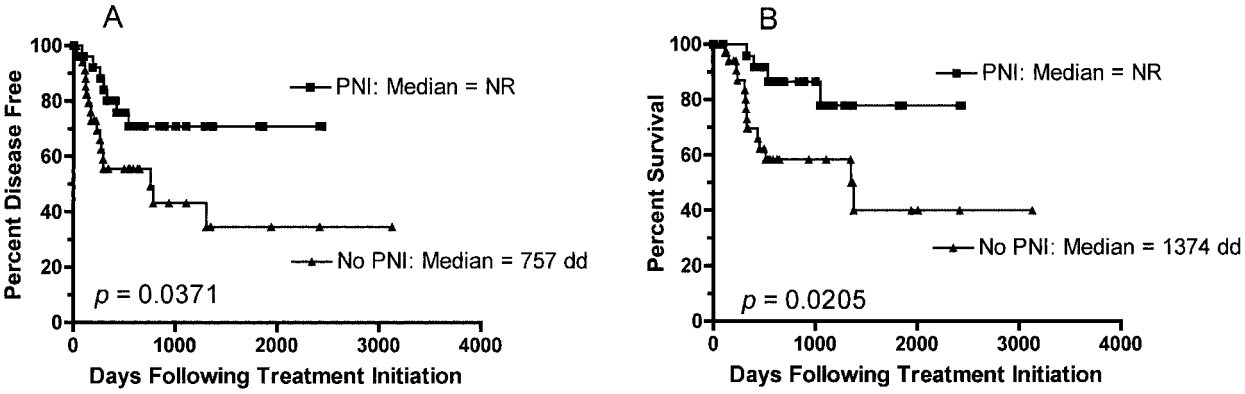

Fig. 1. Kaplan-Meier curves for disease-free interval (A) and survival (B) according to the use of prophylactic nodal irradiation (PNI) in 61 dogs with high-risk mast cell tumours. NR=median not reached.

statistical analysis was repeated evaluating patients with high-grade tumours alone. Mucous membrane location remained a negative prognostic factor for both DFI and OS among patients with high-grade MCT. There was a trend toward increased DFI in patients receiving ALT versus those with microscopic local disease, and there was a trend toward improvement in both DFI and OS for those patients receiving PNI (Table 4).

DISCUSSION

The side effects of prednisone and VBL at the doses used in this study were acceptable, with only 6.5% of dogs developing severe neutropenia necessitating hospitalization or treatment discontinuation. This is similar to the rate reported in our previous study [28]. The demographics of these patients are similar to those reported elsewhere [16, 22].

Adjuvant prednisone/VBL provided longer survival in patients with high-grade MCT than surgery alone has in prior reports (Table 5) [2, 3, 20, 22]; however, it must be acknowledged that comparison with historical controls is a suboptimal method of assessing efficacy, and a randomized phase III study is necessary to definitively demonstrate a survival advantage. A recent report by Hahn *et al.* described a positive outcome in dogs with high-grade MCT treated with RT alone. Of note, all of these dogs received PNI [13]. The results this group obtained are significantly different than those reported by others employing surgery [2, 3, 20, 22, 25]. It is unclear whether their findings represent a unique improvement in outcome as a result of utilizing radiotherapy versus surgery to achieve local control, geographic or statistical variation, or another cause. Despite these findings, the majority of veterinary oncologists feel that local therapy alone is insufficient for optimal control of high-grade MCT.

One noteworthy finding in this study was the significant difference in outcome between patients with "high-risk"

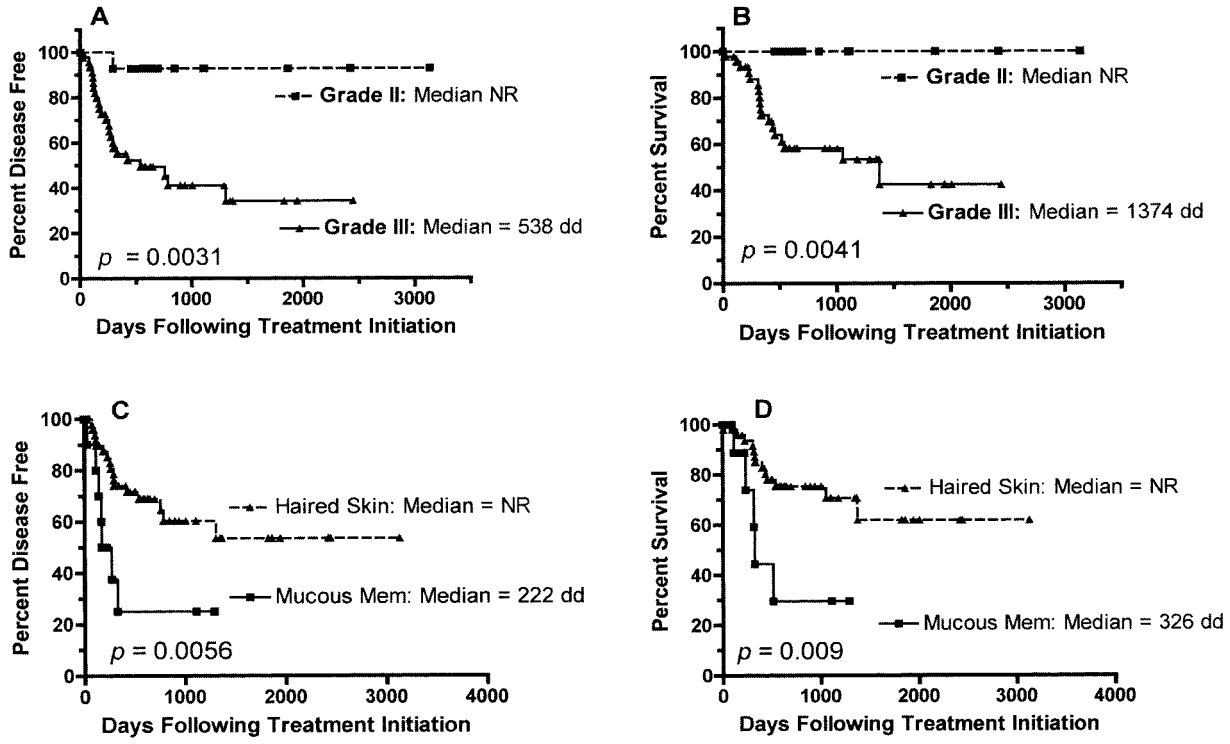

Fig. 2. Kaplan-Meier curves for disease-free interval (A and C) and survival (B and D) according to histologic grade and primary tumour location in 61 dogs with high-risk mast cell tumors. NR=median not reached.

Table 4. Univariate analysis of prognostic variables for effect on disease-free interval and survival for 47 dogs with high grade mast cell tumor treated with prednisone and vinblastine

Variable	Number of dogs	Median DFI	*p* Value[a)]	Median OS	*p* Value
Location					
Muc. Membrane	10	173 d[b)]	326 d		
Skin	37	784 d	0.0101	1374 d	0.0149
Local Treatment					
Microscopic	8	215 d		331 d	
ALT[c)]	39	784 d	0.0614	1374 d	0.2198
PNI[d)]					
No	31	292 d		515 d	
Yes	16	NR[e)]	0.0918	NR	0.0844

a) *p* values were calculated with the generalized Wilcoxon test.
b) d = Days.
c) ALT = adequate local therapy.
d) PNI = Prophylactic lymph node irradiation.
e) NR = Median not reached.

(e.g. node-positive or mucous membrane) intermediate-grade MCT and high-grade MCT. The majority of patients with high-risk intermediate-grade MCT enjoyed long-term tumour control, suggesting that grade may be a more important predictor of behavior than nodal status or location in dogs with MCT. This finding is corroborated by results from Chaffin *et al.*, demonstrating relatively long disease-free intervals in dogs with node-positive intermediate-grade MCT treated postoperatively with RT, with or without oral prednisone, although a higher percentage of dogs in their study eventually relapsed [5].

Upon univariate analysis, histologic grade, mucous membrane origination, and the use of PNI were significant predictors of both DFI and OS. Grade has been shown by many investigators to correlate with outcome in canine MCT [29], and some investigators have likewise suggested that mucocutaneous location may be associated with more aggressive biologic behavior [29, 30]. One report described aggressive

Table 5. Reported survival times of dogs with surgically treated high-grade mast cell tumors

Investigators [Ref. No.]	Number of Dogs	Percent Alive	Months Post Surgery	Median Survival Time (Weeks)
Bostock [2]	45	15	7	NR[a)]
Patnaik *et al.* [22]	17	6	48	NR
Bostock *et al.* [3]	15	27	NR	13
Murphy *et al.* [20]	54	46	12	40
Simoes *et al.* [25]	19	42	20	NR
Current Report	47	58	24	196

a) NR = Not reported.

behavior for MCT of the canine muzzle [11], however it did not specify how many arose from mucous membrane versus haired skin of the muzzle. To our knowledge, this is the first study that has demonstrated a statistical association between mucous membrane origin and outcome in canine MCT.

Some studies have identified tumour size as a prognostic factor in canine MCT [13, 19]. Unfortunately, the majority of patients identified in this study underwent surgery prior to referral, and tumour size was thus often impossible to determine retrospectively.

To our knowledge, this is the first study to suggest that the use of PNI may be associated with improvement in outcome in canine MCT, although this significance was not sustained upon multivariate analysis. The use of PNI is standard clinical practice for selected human tumours such as oral squamous cell carcinoma [9, 21], however its use for the treatment of canine MCT varies between clinician and institution. Two studies of canine MCT in which PNI has been used have been reported [5, 16]: in one, it was unclear as to whether its use impacted DFI or OS [5], and in the other it did not affect outcome [16]. Importantly, both of these studies focused on dogs with intermediate-grade MCT, a population with a generally low metastatic rate. The mechanism behind the observed improved prognosis associated with PNI in our patients is unclear: possibilities include the eradication of incipient metastasis in the irradiated node that are below the limits of cytological detection, or alteration of the LN microenvironment modulating the immune response or interfering with successful LN colonization by tumour cells.

Taking into account the inconsistencies and biases associated with any retrospective study, we conclude that this report supports the adjuvant use of prednisone/VBL in dogs with "high-risk" MCT, as it suggests extended DFI and OS when compared with surgery alone with an acceptable rate of adverse events. A randomized, placebo controlled trial would be necessary to unequivocally demonstrate a statistically significant improvement in outcome.

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FOOTNOTES

[a] Prism, GraphPad Software Inc., San Diego, CA

[b] GB-Stat, Dynamic Microsystems, Silver Spring, MD

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