

Efficacy of Antivascular Photodynamic Therapy Using Benzoporphyrin Derivative Monoacid Ring A (BPD-MA) in 14 Dogs with Oral and Nasal Tumors

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ABSTRACT. Antivascular photodynamic therapy (PDT) suppresses tumor growth and prolonged the survival in solid tumor-bearing mice. The purpose of this study was to assess the efficacy of antivascular PDT using BPD-MA for treatment of oral and nasal tumors in 14 dogs. At 15 min after initiating intravenous infusion of 0.5 mg/kg benzoporphyrin derivative monoacid ring A, tumors were irradiated with laser light at 690 nm emitted by a diode laser. The 1-year survival rate of 7 dogs with oral tumors was 71%. The 1-year survival rate of 7 dogs with nasal tumors was 57%. Imaging of each tumor was performed by using angiographic computed tomography before and after each antivascular PDT. Contrast-enhanced tumors were observed before antivascular PDT, but these tumors were not enhanced with contrast medium following antivascular PDT. Antivascular PDT is suggested to be a promising method for dogs with oral and nasal tumors that cannot be effectively treated with current antitumor therapies.

KEY WORDS: BPD-MA, nasal tumor, oral tumor, photodynamic therapy.

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Photodynamic therapy (PDT) is based on tumor-specific accumulation of a photosensitizer, followed by local irradiation of the lesion with visible light. Selective destruction of tissue occurs when 2 nontoxic elements, i.e., a drug and light, are combined in the presence of oxygen [19]. Photodynamic therapy is a more selective method for cancer treatment than either chemotherapy or radiation therapy. In veterinary medicine, PDT is often selected as a clinical trial method for treating a variety of superficial and localized tumors [6, 9, 32]. Tumors treated by PDT include solid tumors with no metastasis because PDT has no systemic antitumor effects. Canine and feline squamous cell carcinomas (SCCs) are the most commonly reported histological tumor types [20, 32]. Phototoxicity occurs only in the presence of a photosensitizer, molecular oxygen and light of an appropriate wavelength. Upon photoactivation, reactive oxygen species, which have a short lifetime (<0.04 sec) and short radius of action (<0.02 μ m), are generated to induce irreversible damage to cells in the microenvironment [13, 37]. The resulting tumor damage occurs through at least 2 mechanisms—direct cytotoxicity of the neoplastic cells and indirect effects resulting from vascular damage [37]. The relative contribution of the 2 pathways depends on the distribution of the photosensitizer between the cell and tissue compartments, which in turn depends on the properties of the photosensitizer and its mode of delivery. Due to its efficient vascular interactions, PDT is also increasingly used for treatment of noncancerous lesions [14].

Benzoporphyrin derivative monoacid ring A (BPD-MA) is a second-generation photosensitizer with rapid body clearance and strong light absorption at a wavelength of approximately 690 nm, at which the tissue penetration of light is 50% greater than that with porfimer sodium (Photofrin®) at 630 nm [30]. The use of BPD-MA has been approved for treatment of age-related macular degeneration in humans, and its use in cancer treatment is being researched in many countries. Currently, it is in phase II trials for use against multiple nonmelanoma skin cancer [18].

The biological target of PDT using BPD-MA depends upon the interval between drug injection and light irradiation. Photodynamic therapy with a short drug-light interval PDT (15-min interval) targets tumor vasculature and acts as antivascular PDT, while that with a long drug-light interval (3-hr interval) targets cellular compartments. It has been reported that when compared with the latter, the former PDT suppresses tumor growth and prolongs survival in solid tumor-bearing mice [15, 25]. When it is localized within the blood vessels to a great extent, BPD-MA photoactivation leads to damage in the neovascular endothelium, resulting in vessel occlusion by platelet aggregation, fibrin clot formation and vasoconstriction [7, 31]. Therefore, antivascular PDT might be potentially effective for destruction of neovasculture in a solid tumor [15, 25] because angiogenesis is required for tumor growth at both primary and metastatic sites [8].

To the best of our knowledge, there have been no reports on application of antivascular PDT using BPD-MA in veterinary medicine. The purpose of this study was to assess the efficacy of antivascular PDT using BPD-MA for treatment of oral and nasal tumors in 14 dogs.

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Table 1. Summary of patient characteristics

Dog No.	Breed	Sex ^{a)}	Age (years)	Body weight (kg)	Tumor site	Tumor type	Tumor stage ^{b)}	Previous treatment ^{c)}
1	Golden Retriever	SF	7	26.1	Middle mandible	Fibrosarcoma, ameloblastoma	T2bN0M0	–
2	Mongrel	SF	12	13.3	Caudal maxilla	Osteosarcoma	T3bN1aM0	RT
3	Hokkaido Dog	SF	7	21.8	Hard palate	Fibrosarcoma	T3bN2aM0	–
4	Mongrel	CM	9	10.8	Rostral mandible	Squamous cell carcinoma	T1bN0M0	–
5	Miniature Schnauzer	CM	14	8.2	Lip	Fibrosarcoma	T1N2aM0	SR
6	Pekingese	M	10	6.0	Maxilla	Sarcoma	T3bN1aM0	–
7	Golden Retriever	M	11	27.4	Caudal maxilla	Fibrosarcoma	T3aN1aM0	RT
8	Golden Retriever	SF	11	32.4	Nasal cavity	Fibrosarcoma	T1N0M0	RT
9	Golden Retriever	SF	9	28.0	Nasal cavity	Squamous cell carcinoma	T1N2bM0	RT
10	Mongrel	M	15	13.8	Nasal cavity	Adenocarcinoma	T1N0M0	RT
11	Mongrel	SF	10	15.5	Nasal cavity	Neuroendocrine carcinoma	T1N0M0	RT
12	Beagle	M	14	14.4	Nasal cavity	Adenocarcinoma	T3N0M0	RT
13	Mongrel	SF	10	18.6	Nasal cavity	Squamous cell carcinoma	T2N0M0	–
14	Beagle	F	13	10.2	Nasal cavity	Adenocarcinoma	T3N1aM0	RT

a) M, male; CM, castrated male; F, female; SF, spayed female.

b) TNM classification according to the WHO (World Health Organization).

c) RT, radiation therapy; SR, surgical removal.

MATERIALS AND METHODS

Patients and tumors: In the present study, antivascular PDT was used to treat 14 client-owned dogs with naturally occurring head tumors that were brought to the Veterinary Teaching Hospital, Graduate School of Veterinary Medicine, Hokkaido University, between January 2003 and October 2005. The owners did not desire surgery or radiation therapy for treatment of the dogs. Each tumor was diagnosed by histopathological examination of biopsy samples. The patient characteristics are summarized in Table 1. All the dogs were evaluated by complete blood cell count (CBC), serum biochemical profile and thoracic radiographs. Prior to antivascular PDT, no evidence of metastasis was observed on the thoracic radiographs of the dogs. In the present study, the tumor stage was classified using the World Health Organization (WHO) "TNM classification of tumors in domestic animals" [26]. After obtaining informed consent from the owners, the dogs were treated by antivascular PDT. Prior to antivascular PDT, tumor size was documented on the basis of caliper measurements or computed tomography (CT) imaging. The tumor volume was calculated using the formula $(a \times b \times c) \pi/6$, where a, b and c were 3 orthogonal diameters of the tumor. The dogs were followed up for more than 1 year.

Anesthesia and analgesia: Angiographic CT was used to select candidates for antivascular PDT and to subsequently determine the therapeutic effect under sedation after administration of PDT. Sedation was induced by intramuscular administration of a combination of medetomidine (Dormitor®, Meiji Seika Kaisha Ltd., Tokyo, Japan) at a dose of 0.03 mg/kg and midazolam (Dormicum®, Astellas Pharma Inc., Tokyo, Japan) at a dose of 0.15 mg/kg.

Photodynamic therapy was administered under general anesthesia. Flunitrazepam (Silece®, Eisai Co., Tokyo, Japan) was intravenously administered as a preanesthetic

agent at a dose of 0.03 mg/kg. General anesthesia was intravenously induced with thiopental (Ravonal®, Tanabe Seiyaku Co., Osaka, Japan) at a dose of 15 mg/kg and was maintained with isoflurane (Isoflu®, Dainippon Pharmaceutical Co., Osaka, Japan) and oxygen after tracheal intubation. A buprenorphine hydrochloride suppository (Lepetan suppositories®, Otsuka Pharmaceutical Co., Tokyo, Japan) was administered to the dogs rectally at a dose of 0.01 mg/kg after anesthetic recovery. Furthermore, meloxicam (Metacam®, Nippon Zenyaku Kogyo Co., Fukushima, Japan) was administered subcutaneously at a dose of 0.2 mg/kg once daily as an analgesic agent until the day after antivascular PDT.

Drug administration: Liposomal BPD-MA in the form of a freeze-dried powder was kindly gifted to us by QLT Inc. (Vancouver, British Columbia, Canada). It was reconstituted with distilled water before use. The dose of BPD-MA was determined on the basis of the data obtained from a mouse experiment [15, 25]. The volume of reconstituted BPD-MA required to achieve the desired dose of 0.5 mg/kg was diluted with 5% glucose to obtain a total injection volume of 30 mL. After tracheal intubation, the full injection volume was administered intravenously using a syringe pump and an in-line filter with a pore size of 0.45 µm over 10 min at a rate of 3.0 mL/min.

Setting the optical fibers used for tumor irradiation: A quartz fiber fitted with a microlens (Pioneer Optics, Inc, Windsor Lock, CT, U.S.A.) or with a 1.0-, 2.5-, or 5.0-cm cylindrical diffuser at the end (Fibersdirect.com, Kirkland, WA, U.S.A.) was used to ensure uniform light delivery to the tumors. The tumors were irradiated with a 2–4-mm margin for the treatment field to eliminate the possibility of tumor recurrence.

In the case of oral tumors located at the surface, the quartz fiber fitted with a microlens was set toward the surface of the tumor. In the case of nasal tumors, to aid positioning of

Table 2. Response of tumors to antivasular photodynamic therapy

Dog No. ^{a)}	Tumor size (cm ³)	Light intensity (mW/cm ²) ^{c)} (mW/cm) ^{d)}		Light fluence (J/cm ²) ^{e)} (J/cm) ^{f)}		Side effects	Outcome/time to outcome (days)
1	14.1	250		1,275 (17) ^{g)}		Edema	Died of unrelated cause - no tumor recurrence (481)
2-1	37.7	250		800 (8)		—	Tumor remained
2-2	7.6	250		950 (8)		—	Tumor remained
2-3	4.7	250		900 (9)		—	Tumor remained
2-4	1.5	250		300 (3)		—	Tumor recurred (60)
2-5	5.5	250	250	150 (1)	150 (1)	—	Tumor recurred (105) – euthanatized (300)
3-1	41.5		400		525 (7)	Edema, alopecia	Tumor recurred (203)
3-2	2.5		250		200 (2)	—	Tumor metastasis (238) – euthanatized (329)
4	1.1	250		600 (6)		Edema	Alive (951)
5	0.1	250		300 (3)		Edema	Alive (883)
6 ^{b)}	9.6	250	200	800 (16)	200 (2)	Edema	Alive (491)
7	27.5		160, 200		450 (4)	Edema	Alive (470)
8	9.2	250		600 (20)		Edema	Died of unrelated cause – no tumor recurrence (533)
9-1	0.9	200	160	168 (6)	40 (1)	Edema	Tumor recurred (92)
9-2	2.7	250		450 (4)		Nasocutaneous fistula	Tumor metastasis (364) – died of tumor metastasis (691)
10-1	12.6	250	250, 400	50 (1)	500 (4)	—	Tumor remained
10-2	5.5	200	200	350 (4)	300 (4)	Oonasal fistula	Tumor recurred (455) – died (782)
11-1	3.1		160, 200		300 (3)	—	Tumor recurred (162)
11-2	4.2		160, 200		300 (3)	Nasocutaneous fistula, edema	Died of unrelated cause- no tumor recurrence (212)
12 ^{b)}	2.4		160		200 (2)	—	Tumor recurrence (70) - died of tumor infiltration (129)
13-1	30.6		160, 200		300 (3)	—	Tumor recurred (69)
13-2	2.0	200	200	80 (1)	300 (2)	—	Tumor metastasis (319) - died (333)
14	11.8		160, 200		300 (3)	Nasocutaneous fistula, edema	Alive (482)

a) Numbers following a hyphen: the number of times of antivasular PDT.

b) BPD-MA injected 15 min and 3 hr before light irradiation.

c) Light intensity when the fiber was used with a microlens.

d) Light intensity when the fiber was used with cylindrical diffuser.

e) Light fluence when the fiber was used with a microlens.

f) Light fluence when the fiber was used with cylindrical diffuser.

g) Numbers in parentheses: the number of treatment areas.

the optical fiber, the optical fiber was advanced up to the tumor under visual inspection through a rhinoscope or by referring to CT images.

For interstitial irradiation, an over-the-needle intravenous catheter (14-gauge needle) was inserted at the desired location in the tumor mass. The cylindrical fiber was inserted through an external cylinder of the catheter that had been left in place to provide support to the fiber.

Some dogs required irradiation at several sites to completely irradiate the entire tumor, and the irradiated sites were overlapped to avoid the presence of any untreated areas. The surrounding areas that were not included in the irradiation area were shielded from incident laser light by using aluminum foil. Light intensity and fluence, which depend on tumor size, are shown in Table 2. The relationship between the delivered light dose and time is given by the following equation: expression treatment time (sec) = fluence ÷ light intensity.

Antivasular PDT: Fourteen dogs were treated by antivasular PDT to target tumor vasculature. At 15 min after initiating administration of 0.5 mg/kg BPD-MA, the tumor was irradiated with laser light at 690 nm emitted by a diode laser (Coherent Japan, Inc., Tokyo, Japan).

Antivasular and cellular-targeting PDT: Photodynamic therapy that simultaneously targeted both tumor vasculature and tumor cells was administered to 2 of the 14 dogs (Dogs 6 and 12). Dog 6 received an injection of 1.0 mg/kg BPD-MA at 3 hr and 0.5 mg/kg BPD-MA at 15 min before a single irradiation. Dog 12 was administered 2 injections of 0.5

mg/kg BPD-MA at 3 hr and 15 min prior to a single irradiation.

Management after antivasular PDT: The dogs were maintained in a relatively dark room for 24 hr after the BPD-MA injection. In the absence of any untoward event related to general physical condition, the dogs were discharged from the hospital on the next day. CT examination was used to confirm whether tumors persisted or recurred after antivasular PDT. If required, additional antivasular PDT was performed, either once or several times (Table 2).

General physical examination, CBC and serum biochemical analyses were performed on the dogs before and after each antivasular PDT procedure in order to observe the side effects. Dogs were reevaluated every month.

CT imaging of tumors: Imaging of each tumor was performed under sedation or general anesthesia as described before, by using a Hitachi CT Scanner RADIX-PRATICO (Hitachi Medical Co., Tokyo, Japan). Angiographic CT images of tumors were acquired at 1 min after initiating intravenous administration of a nonionic contrast medium. (Omnipaque 300[®], Daiichi pharmaceutical, Co., Tokyo, Japan).

RESULTS

Case details and results obtained after antivasular PDT are presented in Table 2.

Local side effects: Temporary skin edema was observed around the treated area in 10 dogs for a few days after anti-

vascular PDT; however, no particular treatment was required. In Dog 3, mild alopecia was temporarily present at the area of the skin where light penetrated the subcutaneous tissue. In 4 dogs with nasal tumors (Dogs 9–11 and 14), fistulae developed after antivasular PDT. Except for Dog 13, malodorous and purulent nasal discharges were observed in 6 dogs with nasal tumors after antivasular PDT.

Systemic side effects: Some dogs with large tumors exhibited slightly poor activity and appetite after an antivasular PDT; however, these features returned to normal within 1 week. There was a significant increase in the white blood cell (WBC) count at 1 week after antivasular PDT ($p<0.01$); the mean WBC counts before and 1 week after antivasular PDT were $10.4 \times 10^3/\mu\text{l}$ (median, 9.7×10^3) and $17.5 \times 10^3/\mu\text{l}$ (median, 15.5×10^3), respectively. There was a significant increase in the serum alkaline phosphatase

(ALP) activity at 1 week after antivasular PDT ($p<0.01$); the mean serum ALP activities before and 1 week after antivasular PDT were 311.4 U/l (median, 146.0 U/l) and 600.3 U/l (median, 300.2 U/l), respectively. After the second week of treatment, the serum ALP activity decreased to the pretreatment level. Other values in the serum biochemical analyses and CBC did not change significantly after antivasular PDT (data not shown).

Efficacy of antivasular PDT

Oral tumors (7 dogs: Dogs 1–7): In the dogs with oral tumors, the tumors turned black after antivasular PDT. These dogs required surgical removal of the necrotic tissues after the antivasular PDT in order to assist the healing process. The irradiated lesions healed after debridement.

Taking into consideration local toxicity to the eye, Dog 2, which had oral osteosarcoma, was treated 5 times to reduce

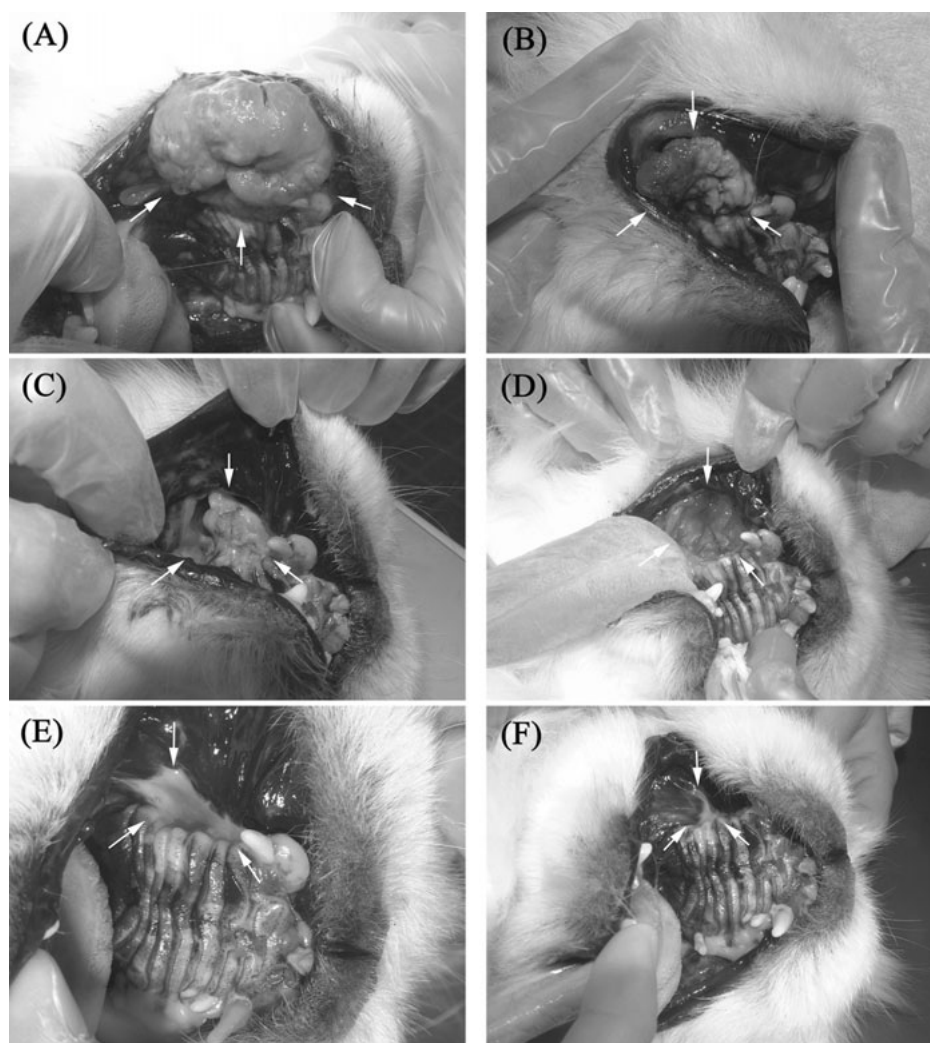


Fig. 1. Dog 6: (A) before PDT (tumor locate maxilla), (B) 5 days after PDT (the tumor is atrophied), (C) 12 days after PDT (necrotic tumor tissue sloughs away), (D) 12 days after PDT (after debridement), (E) 33 days after PDT (an ulcerative lesion) and (F) 96 days after PDT (the treated area is almost completely covered with a normal oral mucosa). Arrows indicate the tumor and treated area.

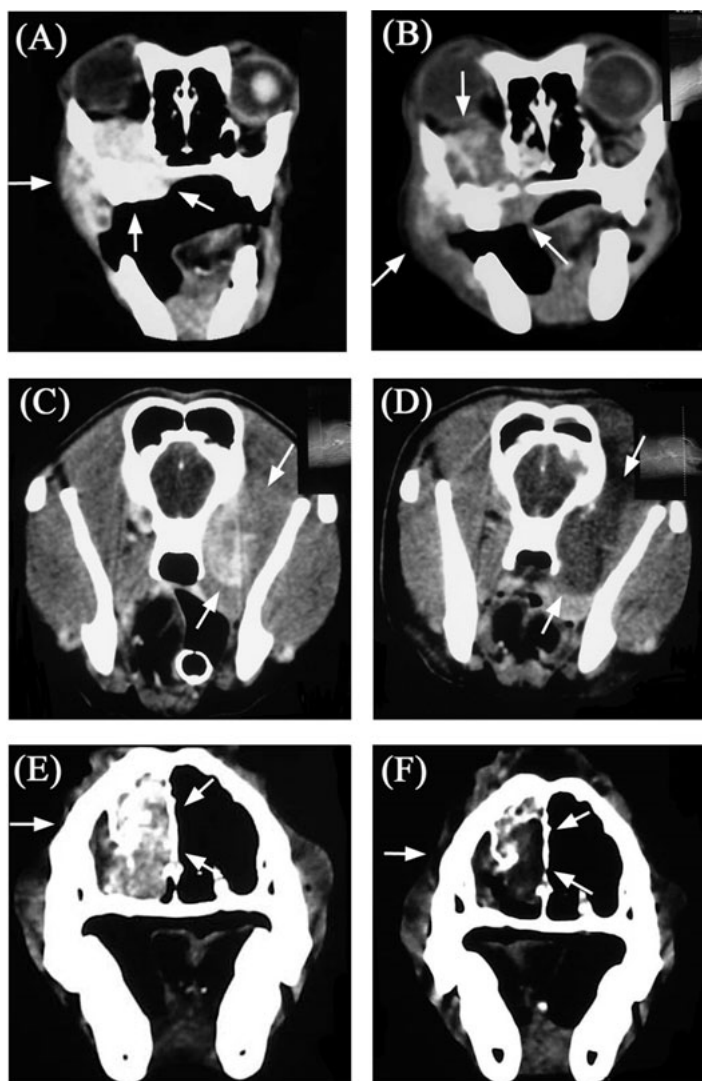


Fig. 2. Selected examples of antitumor response as observed by angiographic CT imaging: (A, B) Dog 2, (C, D) Dog 3, (E, F) Dog 13 and (A, C and E) before antivasular PDT, (B, D and F) on the day after the first antivasular PDT. A contrast enhanced tumor was observed before the first antivasular PDT, but it was not observed after the first antivasular PDT. F shows the turbinated bones that were depressed by the nasal tumor present within the nasal cavity. Arrows indicate the tumor.

the tumor volume. However, a phthisis bulbi associated with the corneal reaction was observed after the fourth antivasular PDT.

The tumor in Dog 6 (Fig. 1) became atrophied and necrotic after antivasular PDT, and it was debried 12 days after antivasular PDT. Although an ulcerative lesion persisted 33 days after antivasular PDT, the treated area was almost completely covered with a normal oral mucosa at 96 days after treatment. The last follow-up at 491 days after treatment revealed that the tumor had not recurred.

Nasal tumors (7 dogs: Dogs 8–14): In regard to nasal tumors, the tumors were not enhanced with contrast medium

after antivasular PDT.

In 6 dogs with nasal tumors, with the exception of Dog 10, tumor size remarkably reduced after antivasular PDT. In dogs 9, 11, 12 and 13, tumors recurred at 92, 162, 70 and 69 days after antivasular PDT, respectively.

In Dog 10, irradiation was initiated 40 min after BPD-MA administration. Subsequently, the tumor size in Dog 10 slightly decreased after treatment. Since tumor regrowth occurred, a second antivasular PDT was performed 139 days after the first antivasular PDT. At 28 days after the second antivasular PDT, oral examination revealed an oronasal fistula. However, tumor recurrence was confirmed

455 days after the first antivasular PDT; however, metastatic lesions were not observed. The dog died 782 days after administration of the first antivasular PDT.

CT imaging of tumors: The angiographic CT images obtained before antivasular PDT demonstrated homogeneous enhancement without necrosis and liquefaction (Fig. 2-A, C and E). The angiographic CT images obtained after antivasular PDT demonstrated that the tumors were not enhanced with the contrast medium (Fig. 2-B, D and F).

Survival rate: The 1-year survival rate of the 7 dogs with oral tumors was 71% and that of the 7 dogs with nasal tumors was 57%.

DISCUSSION

Currently, there is no data available on the appropriate indications and safety in application of antivasular PDT for solid malignant tumors in companion animals. In our present study, dogs with oral and nasal tumors were treated by antivasular PDT. Our study has shown that antivasular PDT using BPD-MA was considerably effective in treating oral and nasal tumors.

In this study, the incidences of edema and fistula were 71% (10/14) and 29% (4/14), respectively. Temporary edema was observed around the irradiated area, which appeared to be well tolerated. In dogs with nasal tumors treated by radiation therapy, fistulae were observed after antivasular PDT. The incidence of radiation injury was 83% (5/6) before antivasular PDT. Radiation therapy can enhance the rate of BPD-MA uptake by the vascular endothelium [23]. Furthermore, radiation injury may have an effect on the rate of BPD-MA uptake. In the present study, dogs treated with antivasular PDT following radiotherapy had a substantial risk of developing post-treatment complications such as chronic or recurrent rhinitis and fistula. Six dogs treated with antivasular PDT after radiotherapy developed rhinitis, and this might have been associated with tumor necrosis. The malodorous and purulent nasal discharge was improved by removal of necrotic tissues and washing of the nasal cavity. The dogs treated with antivasular PDT are currently being treated with antibiotics to reduce the incidence and severity of bacterial rhinitis. In contrast to radiation therapy, late injury was not observed after this treatment.

The results of the blood examination revealed a transient increase in serum ALP activity; this might be associated with the hepatobiliary elimination of BPD-MA [11] and/or bone necrosis induced by antivasular PDT. Some of the dogs with a large tumor exhibited slightly poor activity and appetite after antivasular PDT. This was probably related to massive tumor necrosis. However, these features returned to normal within 1 week. Bacterial infection following tumor necrosis could not be ruled out because the WBC counts had increased. Therefore, broad-spectrum antibiotics (typically ampicillin sodium) were orally administered until evidence of clinical improvement was obtained.

The current recommended therapy for treatment of oral

tumors is resection of the mandible or maxilla to ensure tumor-free surgical borders. Surgical excision can be effective, but it might be too aggressive to avoid local recurrence. Furthermore, it might be cosmetically and functionally undesirable. Dogs with oral SCC have a median survival time of 3.5 to 19.2 months [28, 29, 38], and the 1-year survival rate is 57% to 84% [38, 39]. Dogs with oral osteosarcoma have a median survival time of 4.6 to 17.6 months [28, 29, 33, 38], and the 1-year survival rate is 17% to 59% [28, 29, 33, 38, 39]. Dogs with oral fibrosarcoma have a median survival time of 9.5 to 12.2 months [28, 29, 33, 38], and the 1-year survival rate is 50% [33]. Most of these reports have suggested that histologically complete resection and rostral location of mandibular tumor are favorable prognostic indicators. Radiation therapy is generally recommended for unresectable tumors. The mean survival time in fibrosarcoma and malignant melanoma cases was approximately 7 months. However, most dogs suffer from side effects of radiation therapy, such as alopecia, mucositis, skin fibrosis, keratoconjunctivitis sicca and bone necrosis [4, 35].

In the present study, the 1-year survival rate of 7 dogs with oral tumors was 71%. A previous study reported a median survival time of 29 months in dogs with oral tumors treated by surgical debulking followed by PDT with hexylpyropheophorbide. Almost all these tumors were smaller than 4 cm in diameter and were located rostrally at the mandible [4]. Treatment of these tumors by antivasular PDT might have been a relatively less invasive treatment option offering a prognosis identical to that obtained by surgery. Oral tumors can be easily irradiated under visual inspection, and gingival SCCs do not readily metastasize; therefore, oral SCC is a particularly good candidate for PDT [20]. In the present study, although some dogs had surgically resectable tumors, antivasular PDT was minimally invasive. In Dog 6, the tumor did not recur after PDT targeting cellular and vascular compartments. In a previous study of murine mammary adenocarcinoma tumors (MCAIV cell lines), the combination of PDT with short and long drug-light intervals (15-min and 3-hr intervals, respectively) enhanced the anti-tumor effects by damaging both the tumor vasculature and the cellular compartments [5]. Since 2 injections were required to administer the photosensitizer, the drug dose required for the combined PDT was increased to enhance the effects. Therefore, only small dogs were treated with the combined PDT method. This novel method of employing a combination of PDT is considered to be more practically effective for treatment of tumors.

In present study, in all the dogs with oral tumors, tumor necrosis was observed after antivasular PDT using BPD-MA. The necrosis led to exposure of the bone invaded by the tumor. Healing of the treated area occurred rapidly after removal of the necrotic bone. Two dogs (Dogs 2 and 3), whose tumors had invaded the bones, developed oronasal fistula after antivasular PDT, and an oesophagostomy tube was placed. The tumors that extensively invaded the bone might have been destroyed due to the cutting off the blood supply. PDT is a selective treatment, and excellent tissue

healing is a valuable advantage of PDT. If necessary, the necrotic tissues were eliminated to encourage healing. Antivascular PDT was not considered to be more invasive than surgery; however, it is selectively and minimally invasive.

The median survival times of dogs with intranasal tumors treated by surgery or chemotherapy and of those without any treatment range from 3 to 6 months [10, 22]. External beam radiation therapy is presently considered to be a standard treatment for intranasal tumors, and the 1-year survival rates of dogs treated by radiation therapy range from 38% to 60% [1, 34]. Local tumors recur in 68% of dogs with a median relapse-free interval of 270 days [2]. In another study, 33% of the dogs in a radiotherapy-only group were euthanized within 10 months of radiotherapy because of local recurrence [3]. Many owners might elect not to treat dogs and cats with intranasal tumors because of the distance between their residence and the veterinary radiation therapy facility and due to their concerns regarding multiple anesthesia events. Similarly, the potential for side effects during and after radiation therapy, such as moist desquamation, keratoconjunctivitis sicca, cataracts, surgical wound dehiscence and nasal osteonecrosis, may also deter some owners [1, 34].

In the present study, the 1-year survival rate of the 7 dogs with nasal tumors was 57%. In dogs with nasal tumors, with the exception of cases of terminal cancer and death due to unrelated causes, it has been considered that the results of antivascular PDT are parallel to that of radiation therapy [1]. Antivascular PDT using BPD-MA for treatment of nasal tumor led to better results than PDT using pyropheophorbide-a-hexyl ether [17]. The adenocarcinoma in the nasal cavity of Dog 10 recurred easily; this was believed to be due to reduction of the effect of antivascular PDT caused by delay of the start of irradiation after the BPD-MA injection. Considering the pharmacokinetics of BPD-MA [24] and the results of the present study, we believe that the concentration of photosensitizer in the blood dropped to a lower level during irradiation (data were not shown). Although antivascular PDT was selective and effective, considering its influence on surrounding tissues, tumors near the brain cannot be irradiated. Therefore, some of the dogs had multiple episodes of PDT because of recurrence. Most radiation therapy regimens are fractionated. The rationale for fractionation of radiation therapy lies in the potential for a differential response of tumor cells as opposed to normal tissue [21]. However, tumors can be treated by antivascular PDT in the event of recurrence. When tumors persisted or recurred after the first antivascular PDT, additional antivascular PDT was carried out.

The accuracy of the fiber tip placement can be improved using a flexible endoscope or CT. The ability to effectively deliver light through fiber optics directly to the tumor mass not only preserved the normal tissue to a great extent but also effectively irradiated the deeply localized tumor tissue. Furthermore, these diagnostic imaging methods enable detection of the presence or absence of tumor recurrence in the nasal cavity after antivascular PDT.

Since tumor angiogenesis is crucial for tumor growth, progression and metastasis [8, 27], it can be used as a prognostic indicator to decide the treatment protocol. In previous studies on breast and liver cancer, angiographic CT or magnetic resonance imaging revealed that the degree of contrast enhancement of a lesion depended on the vascular density of the lesion as well as the permeability of the microvasculature [12, 16, 36]. Imaging of each tumor was performed by using angiographic CT before and after each antivascular PDT. Contrast-enhanced tumors were observed before antivascular PDT, but these tumors were not enhanced with contrast medium following antivascular PDT. Poor perfusion means vascular shutdown leading to tumor hypoxia and necrosis. The sample size used in the present study is small; therefore, the data might be inadequate for comparison of the CT enhancement values with the clinical outcome. Further investigation of malignant tumors in dogs is required to accumulate more meaningful information in regard to tumor response to antivascular PDT.

Antivascular PDT can be completed in less time than cellular-targeting PDT, and the BPD-MA dose required in antivascular PDT can be less than that required in cellular-targeting PDT [15]. Since elimination of BPD-MA is rapid [24], antivascular PDT can be repeated, if necessary, for a residual tumor or in the case of recurrence.

Antivascular PDT is suggested to be a promising treatment for dogs with oral and nasal tumors that cannot be effectively treated with current antitumor therapies. This therapy should be considered as a possible treatment in canine solid malignant tumors. Moreover, angiographic CT might play an extremely useful role in determining the therapeutic effect after antivascular PDT.

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